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No 1



MEDICINE IN THE NATIONAL DEFENSE PROGRAM

IRVIN ABELL, M D

LOUISVILLE, KY

SINCE THE MEMBERS of the Southern Surgical Association are all members of the American Medical Association, I felt that you would be interested in knowing of the work of its Committee on Military Preparedness. This Committee was appointed at the session of the House of Delegates in New York in June, following a request of the Surgeons-General of the Army, Navy, and Public Health Service that the American Medical Association undertake a survey of the profession in the United States regarding the qualifications and availability of its members for service.

There are 179,000 doctors entitled to practice in the United States by means of legal registration, and a questionnaire was sent to each of these. Between 140,000 and 145,000 are in active practice, while the remainder have retired because of age disability, or having sought other pursuits. So far, 125,000 replies have been received, of which over 75,000 have been transferred to punch-cards. These punch-cards contain the information furnished by the questionnaires, and by using them in the International machine, one may in a few minutes get a list of qualified men in any given branch of medicine. This work has been undertaken by the American Medical Association as a patriotic contribution to the National Defense Program, and has entailed the employment of an additional 16 persons in the American Medical Association's office. It is hoped that within two or three months information will be at hand upon every doctor in the country. The only exemption in the Selective Service Act applies to students of theology and accredited ministers of the gospel. Deferments will be made to students in accredited schools, pursuing a course of study leading to a degree in Arts and Sciences, and, also, to those who occupy essential positions in their community. In order to effectively safeguard the health of the population and to furnish medical service to the armed forces, the medical profession feels very strongly that medical students should be permitted to finish their undergraduate education and, at least, one year of internship before being inducted into service. The Selective Service Act, however, provides deferment for students only until June, 1941, after that date any deferment granted

to medical students, to interns, and to residents, will be the responsibility of the local Draft Boards. While doctors should be willing to make such adjustments as may be needed in the event of an emergency, it would be unfortunate if in the Defense Program the classes of medical schools, the teaching program of medical schools, and hospital service should be disrupted by an undue number of students, interns, and residents being called into service. This can be avoided only by applying to the local Draft Boards and to the Appeal Boards for the deferment of those essential to these three activities. There are approximately 15,000 members of the Medical Reserve Corps, and these will be largely drawn upon to furnish medical service for the first increment of selectees. It is estimated that by July, 1941, the total strength of the army will be approximately 1,400,000 men, for which the services of 10,000 doctors will be required. The length of service of the vast majority of doctors will be one year, at the end of which time they will be transferred to the Reserve Corps on an inactive status. The information being gathered by the Military Preparedness Committee of the American Medical Association will make it possible to employ the services of doctors in positions for which their training and qualifications fit them, and thus to avoid some of the mistakes and misfits which occurred in the First World War.

The major objectives of the survey are to provide medical service for the armed forces, to provide medical service for industrial mobilization, and to provide continuing medical service for the civilian population. In the First World War more than 32,000 physicians voluntarily served with the armed forces. In the event of war coming to our country again, the profession will similarly give of its members a sufficient number to meet the needs of the Army, Navy, and Public Health Service. Furnishing medical service to the rapidly expanding industrial plants presents many difficulties, it will be no task to supply doctors who are fully competent to care for industrial injuries, but it is quite another problem to supply doctors familiar with the toxicologic problems of industry. Practically all of the metals, many of the solvents, such as benzol and tuluol, and many chemicals used in industry are capable of producing rather disastrous toxic effects upon the human organism. To effectually control these hazards requires the cooperation of the physician who is familiar with the problems and the safety engineer who understands methods of prevention. Continuing the service to the civilian population through hospitals and through men in various fields of practice is essential if the health and welfare of the civilian population is to be protected.

On September 19, 1940, President Roosevelt appointed a Health and Medical Committee, a subcommittee of the National Defense Council, its members are Surgeon-General McGee of the Army, Surgeon-General McIntyre of the Navy, Surgeon-General Parran of the United States Public Health Service, Dr. Lewis Reed, Chairman of the Medical Division of the National Research Council, and your humble servant, representing the

civilian profession. The duties of this Committee are to advise the National Defense Council on health and medical matters affecting National Defense and to coordinate all health and medical efforts. The Medical Division of the National Research Council has at present 38 committees, each studying some problem in its relationship to Military Medicine, such for instance as shock, chemotherapeutic treatment of wounds, blood transfusions, aviation medicine, tuberculosis, neuropsychiatry, nutrition, *etc.* The Health and Medical Committee has appointed subcommittees on dentistry, medical education, hospitals, nursing, industrial health and medicine, and Negro health. An effort has been made to secure the advice and help of those whose qualifications in their respective fields entitle them to serve with advantage to the country.

It gives me much pleasure to gratefully acknowledge the unanimous offer on the part of the profession at large, of the various National and Special Medical Societies, of the hospital groups, in fact of all agencies relating to health and medicine to cooperate fully and freely in the Defense Program.

This paper was read before the Fifty-third Annual Session of the Southern Surgical Association, Hot Springs, Va., December 10, 11, 12, 1940.



SCIENCE AND HUMAN PROGRESS—IV

Radium and Atoms

DALTON'S Atomic Theory and Mendeleeff's Periodic Law developed the idea that all matter was composed of a limited number of kinds of indivisible building bricks, known to us as the atoms of the elements, out of which all things are constructed. While these concepts were indispensable as stepping stones to a better understanding of the structure of matter, they seemed to close the door to the possibility of anything outside of the material.

The discovery of radium smashed these bricks and transformed them into little constellations with a central nucleus, about which revolved electrons at infinitesimal but relatively great distances from the nucleus. This opened the door to a better understanding of forces, probably enormously more important to the ultimate destiny of Man than the material benefits which have already so magnificently followed the discovery of radio-activity in all its present applications. The unbelievable results derived directly from the discovery of roentgen rays are too apparent for emphasis.

—A. Cressy Morrison, Transactions of the New York Academy of Sciences, Series II, 2, No. 3, January 1940.

THE TREATMENT OF FRESH TRAUMATIC WOUNDS

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THE SUCCESSFUL SURGERY of traumatic wounds is far more exacting of judgment, skill, and time than is elective surgery. This is readily understandable because in the case of such wounds the surgeon begins his work with damaged, soiled, and contaminated tissues rather than with healthy, clean, and sterile tissues which he encounters in elective surgery. It is to us totally nonunderstandable that this difficult problem elicits so little real interest on the part of leaders of surgery in this country and is commonly delegated to the younger inexperienced surgeons to deal with hurriedly. This erroneous attitude may, in a large measure, be due to the fact that traumatic wounds are not made by the surgeon (at least they are not supposed to be) and, thus, the responsibility for the result can so easily be blamed upon factors other than the judgment and skill of the surgeon. It is not only easy but a great temptation for a surgeon to ease his conscience by ascribing to God or influences beyond his control his tragic results of treatment of traumatic wounds. The reverse attitude is, of course, the correct one, the fact that the surgeon did not make the wound should be a superchallenge to him to use the greatest judgment and skill which his knowledge affords him and his poor results should never fail to hurt his pride and teach him something.

We want to pursue this thought a little farther, before going on with our paper, by citing a few glaring examples of what we have been discussing. While the most trivial elective surgical problem is being treated in the main operating room under the most rigid surgical precautions, you will often find far more serious, soiled and contaminated traumatic wounds being treated improperly, under trying and questionable circumstances, in the Out-Patient Clinic. Is there any logic in this when, with the exercise of more care, patience, and skill, under the conditions obtained in the general operating room, such wounds may be made to approach the cleanliness and sterility of the elective case? The answer is unequivocally "no," when the dirty, contaminated wound is on your son or the son of any other doctor who knows not only the importance of but the surgical skill required for rendering the proper toilet and repair of such wounds.

Recognizing the tendency as well as the temptation to extend the services of the accident room to include so-called minor traumatic wounds which we do not at all regard as minor, we have found it advisable to make certain rules regarding the cases which may or may not be treated in the accident

department. For example, no open wounds which may have involved tendons, nerves, bone, important blood vessels, or may have pierced any of the cavities of the body can be treated there. Except for the control of hemorrhage, in the performance of which we decide the use of the tourniquet, and the general treatment of shock, we demand that such wounds be rigidly left alone until the proper type of treatment can be carried out in the main operating room. The wound is simply covered with dry gauze and immobilized until the operating room is ready and the patient is in condition to be taken there. Any half-hearted attempts at the cleansing or sterilization of such wounds in the accident room is strictly forbidden. It is inexcusable to yield to the temptation to pull a protruding end of bone back beneath the skin. In other words, we believe the first chance at the toilet of a traumatic wound is the all-important chance. When a surgeon secures this chance within the period of contamination (six to eight hours), we are not very sparing of our criticisms if he attempts to secure primary healing of the wound and fails.

We have come to believe in, and have adopted, certain fundamental principles regarding the treatment of traumatic wounds. Most of them are very old and the value of many of them was first clearly demonstrated during war-time experiences. It may be well to review briefly those principles.

(1) *Hemostasis or the control of hemorrhage* is certainly the oldest and one of the most fundamental. Its importance was obvious and remains so to-day. It appears to us, now, that for centuries this was about the only worthwhile principle clearly in the minds of those who treated wounds even though their efforts to practice it were often harmful and inhuman. In the light of our present knowledge, it seems that their efforts to promote wound healing, by ointments and concoctions, could have been of little or any benefit.

(2) *The prevention of, or the elimination of, necrotic tissue, débris, and foreign bodies in wounds* was the next fundamental principle of wound treatment to emerge. It is true that Paracelsus, and others had recognized it but it was Paré, who, over 400 years ago, brought it forcibly to the attention of the medical profession. He stopped many of the efforts to control hemorrhage, which were violating this principle. The importance of this principle was immeasurably strengthened and the technic of observing it vastly improved during the World War (1914-1918). It is now firmly established under the name of "*débridement*."

(3) *The value of rest or immobilization of wounds* was particularly stressed by Baron Larrey in the Napoleonic wars. In recent years, a revival of interest in this principle of therapy has been due largely to Winnett Orr and Koch, its value was unquestionably demonstrated by the Spanish military surgeons, particularly J. Trieta, during their recent civil war. What is not yet as generally recognized or practiced, as it should be, is that immobilization is just as valuable in the treatment of soft tissue wounds as it is in the treatment of wounded bones.

(4) *Efforts to control infection in, or to eliminate contamination from, fresh traumatic wounds does not justify the use of substances which are injuri-*

ous to living cells This we know is a debatable point, and we state, for what it is worth, our position, which is that we know of no antiseptics which we are willing to put into fresh wounds

(5) *The preservation of a proper blood supply* to wounds is vitally important and not only from the mere necessity of trying to avoid sloughing. When our conception of this principle is enlarged from the narrow one of the actual amount of blood flowing to the tissues of a wound to include the character and quality of blood supplied to the wound, there arise considerations not dreamed of until within recent years. These involve the use of blood, blood plasma, fluids, electrolytes, vitamins, proteins, *etc*, all in an effort to restore to the patient and, consequently, to his wound an essentially normal blood which we know to be a great aid to wound healing. Besides, there are relatively simple means of determining the deficiencies of these various substances in the blood. We must know them, we must use them whenever possible, we must learn more accurately to recognize clinically these deficiencies when the laboratory aids are not at our command.

(6) It is essential to have some clear-cut conception of the difference between *bacterial contamination and bacterial infection* of a traumatic wound. The former we regard as a surface involvement with very little bacterial proliferation or invasion, the latter as an invasive process with definite bacterial proliferation.

(7) *Fresh wounds, surgical or traumatic, are rarely, if ever, absolutely free of bacteria, then sterilization is relative*

(8) *Granulation tissue is essential to the healing of all wounds*. In the absence of the body surfaces' normal protection, it is nature's best protection against infection.

(9) *The healing of wounds is brought about by the growth and activity of living cells, save for what is accomplished by contraction*. Some knowledge of tissue culture makes this principle far more valuable and understandable.

(10) *Tetanus and gas bacillus antitoxin* should be used prophylactically whenever the nature of the wound and the severity of its soiling indicate their use. Here it is difficult to make any hard and fast rules. With us, the matter is largely determined by our satisfaction with the thoroughness of the debridement or the toilet of the wound. When we feel justified in an attempt at primary closure of the wound we are less inclined to use either one of them.

(11) More or less as corollaries or amplifications of some of the above principles, it should be stated that *healthy living cells have a remarkable power to combat bacteria, that dead or devitalized tissues are powerless against their onslaught*, that prior to the lapse of six to eight hours the bacteria in a fresh wound may be considered as being on the surface of the wound and not invading the living tissue, that the position of a wound may be an important factor in its blood supply, that dressings and the temperature may influence the blood supply and the growth of living cells, *etc*.

This declaration of faith in certain principles which guide us in the treatment of traumatic wounds is not sufficient, for it is obvious that a slave-like

devotion to some of them cannot help but mean a sacrifice of certain others. For instance, the overzealous devotee of hemostasis can easily violate the principles of débridement. It is, therefore, proper that we should tell you in more detail how we attempt to make use of them.

When the patient is first seen, no attempt is made to do anything to the wound except to control hemorrhage, if this is necessary. We prefer to do this by placing firm pressure on the wound with the hand, through the medium of a sterile dry sponge while at the same time elevating the part. If there is a rather large active bleeder, this can often be stopped by direct pressure with the point of the finger until a ligature or clamp can be applied to it. Sometimes mediate pressure with the finger on the main artery away from the wound will accomplish the same thing. We prefer, if possible, never to use the tourniquet simply for the emergency control of hemorrhage, unless upon so badly mangled extremities that they must obviously be amputated. Then, the tourniquet is placed so close to the wound that there will be little or no unnecessary loss of the part when the amputation is done. During the control of the hemorrhage if there is other available professional help, the degree of shock should be assayed and efforts set in motion to combat it. With these things accomplished or underway it is time to take "time out" and consider carefully what the next steps should be. The surgeon might ask himself innumerable questions.

What does this patient's condition warrant doing? Is it safe or wise to remove the patient to the hospital, or from the accident room to the operating room, and how shall the wound be immobilized during the process? If serious shock has been combated will there be similar means of combating it (blood plasma, fluids, etc.) at the destination of his transport and during any operation which might be decided upon there? Is it being borne in mind that, though this patient has at the moment been brought out of shock, he can go back into shock with alarming rapidity during manipulation or operative procedures? If it is assumed that the wound and the patient's condition justify some operative procedure then one should ask himself some other questions. Shall this wound be regarded as contaminated or as infected? Is it a simple incised wound which needs only cleansing and repair? Is it so soiled and traumatized that it should be completely excised (débridement), cleansed, and primarily closed or skin grafted? Are there damaged vital structures such as nerves, tendons, and blood vessels which will prohibit a complete debridement but will permit sufficiently satisfactory cleansing to justify preparations for an attempt at delayed primary suture or grafting? Are the nature of the wound and the circumstances of its occurrence such that only the points of entrances and exit should be treated and the wound immobilized? Is the wound so obviously infected and soiled that it should be treated only with the idea of secondary closure, of later skin grafting on the granulation tissue, or of allowing it to heal spontaneously? After deciding what is ideal, the surgeon must decide what is practical with the facilities at hand and the conditions under which he must work.

With a belief in the fundamental principles of treating fresh traumatic wounds as we have enumerated them, we do not often have any difficulty in answering the above questions so far as the wound is concerned. With facilities for determining the hematocrit reading, the blood proteins, the fluid and electrolyte needs and with blood, blood plasma, and other solution always ready for immediate use, the answer to these questions from the point of view of the patient's status is not nearly so difficult as it used to be.

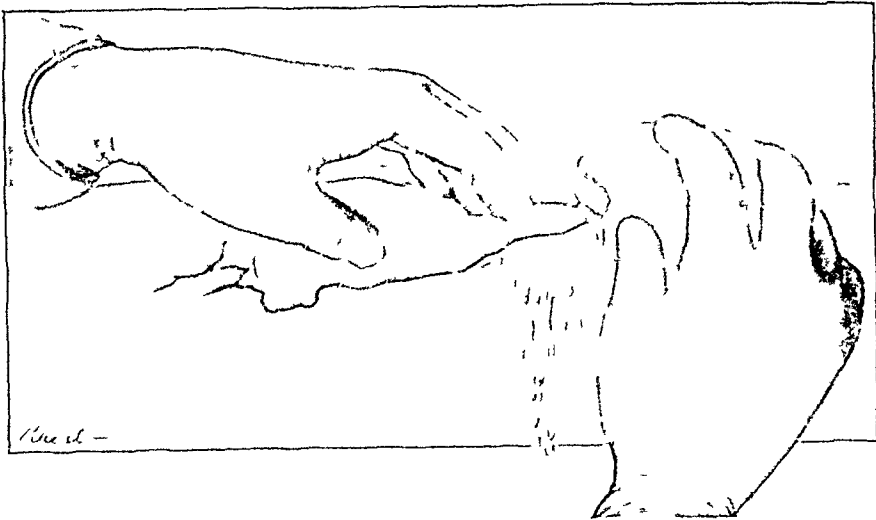


FIG. 1—A sponge has been tucked into the wound so as not to overlap the adjacent skin. The area has been shaved and is being washed for ten minutes with soap and water. This will be followed by alcohol and ether skin preparation.

Let us take a few examples to illustrate in more detail just what we do with different types of wounds.

(1) *A simple incised and contaminated wound.* By this we mean a wound of less than eight hours' duration in which there is no discernible damaged or devitalized tissue which requires debridement.

The operator scrubs up and puts on gloves. A dry sponge is placed in the wound so that it will not overlap the edges. The skin in the field of operation is shaved, then thoroughly scrubbed with soap and water for ten minutes up to the edges of the wound, all grease and dirt having been removed with benzine or ether. The skin is now cleansed with alcohol and ether, and then painted with tincture of merthiolate. None of the benzine, alcohol, ether or merthiolate is permitted to enter the wound. Gloves are changed and the wound draped as though for a sterile operation. The wound is then anesthetized with novocain introduced well away from the wound. Following this, the sponge is removed and every recess of the wound carefully inspected for foreign bodies which should be removed. If there is no grease or staining of living tissues which may require the use of soap and water, the wound is carefully washed with normal salt solution, using the gloved finger for gentle rubbing of the raw surfaces. When the cleansing is complete so that all tissues look clean, healthy, and normal, the wound is again copiously irrigated with normal salt solution. The skin is again dried and recoated with merthio-

late. Gloves are again changed and new drappings applied right up to the edges of the wound. The repair of the necessary deep structures and of the skin is made throughout with silk sutures. It should be added that a minimum amount of silk is used for the ligatures of blood vessels and the suturing of fascial planes. Severed tendons and nerves, and occasionally large blood vessels are accurately approximated with it. After closure of the skin, which may be by primary suture or with the aid of grafts and always without drains,

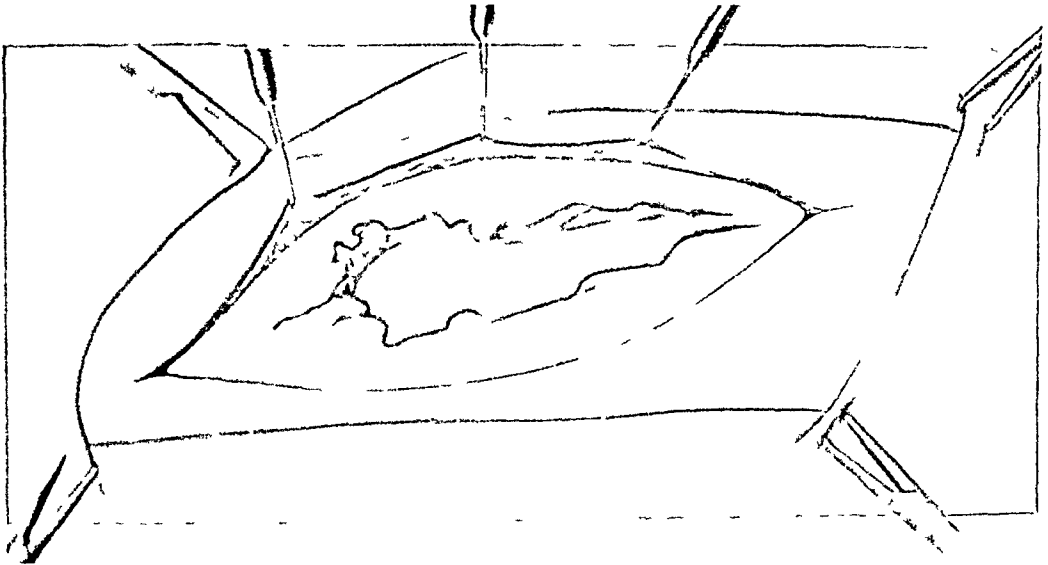


FIG. 2.—The skin has been painted with a skin antiseptic up to the wound edges and draped. No skin antiseptic and no alcohol, ether or soap has been allowed to enter the wound. The excision of the wound has been started.

the wound is dressed with a moist saline gauze and, if possible, completely immobilized. The wound is not dressed until there is some indication for doing so. This might be at the end of three days or more than three weeks, depending upon the possible harm of movement incident to the dressing. The indications for dressing the wound are pain, unexplained fever, impaired circulation to the part beyond, or the necessity of removing stitches. Blood or serum-stained dressings are no indication that the dressing should be changed.

(2) *Delayed primary closure of an incised wound of such duration that it can no longer be regarded as simply contaminated—one which must be regarded as infected although there is no evidence of active suppuration, inflammation, or the formation of granulation tissue.* In this connection, it should be remembered that such wounds about the head and face may be regarded and treated as only contaminated for a much longer period of time than is the case when they occur in other parts of the body.

When, however, a delayed primary closure is decided upon, the procedure is as follows. The steps are exactly the same as just described above, up to the point of repair of the wound. Instead, it is packed loosely in all its recesses with moist saline gauze which is covered with gutta-percha to keep it moist. It is then immobilized for 24 or even 48 hours. On the removal of the gauze pack, if the wound appears healthy, clean, and uninfamed, it is

repaired as though the delay had not occurred. If it is obviously infected or otherwise unfit for closure, the surgeon's course should be planned toward securing healing with the aid of an open granulating surface.

This delayed primary closure is often a useful procedure when what would otherwise be a primary closure has to be terminated because of the patient's condition.

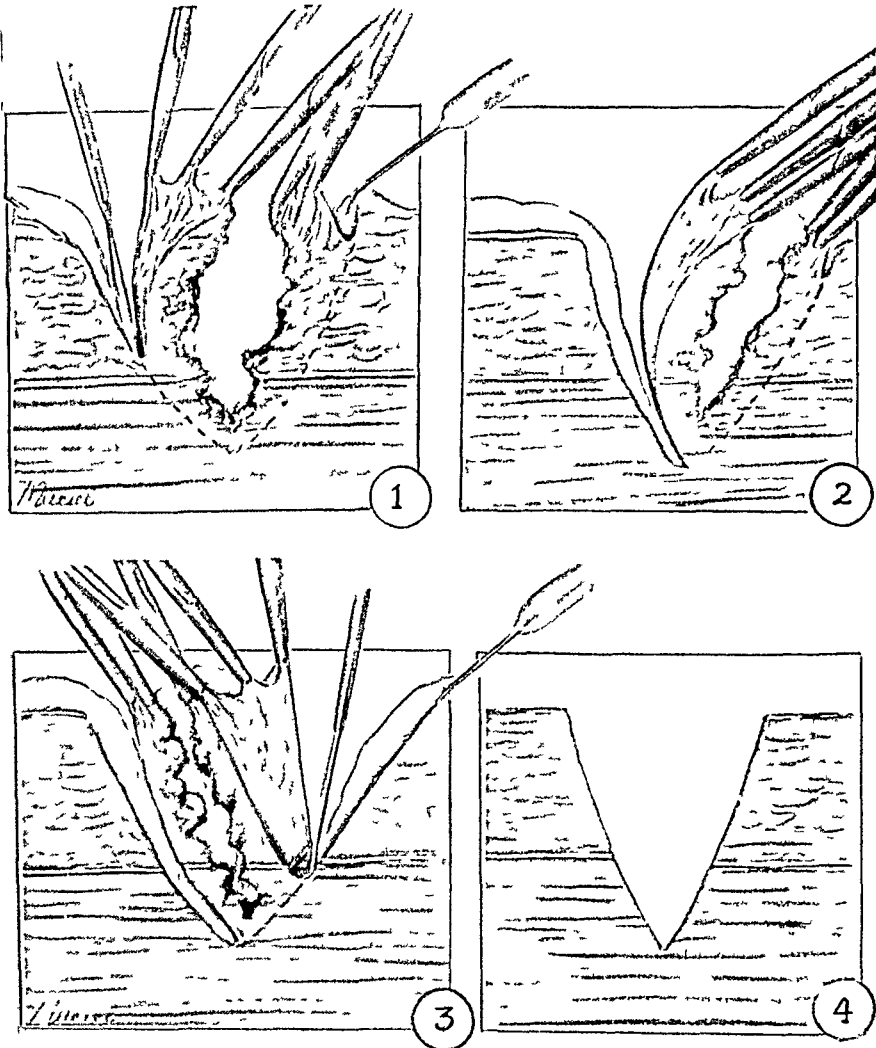


FIG. 3—(1) Hemostats have been applied to the skin edge which is to be excised. The excision has been carried down to the muscle. Fresh pads moistened with saline have been advanced down the clean side of the wound as the incision is deepened. (2) The excision has been completed on one side. Note the protection by the gauze pad. (3) The excision has been nearly completed. (4) The completed excision. The wound is now irrigated copiously with normal salt solution and fresh drapings are applied.

(3) *Treatment of the superficial point of entrance or the points of entrance and exit of a wound plus immobilization.* Quite often in civil life and to a lessening extent in military life, there will occur stab, rifle or pistol wounds or even fractures, compounded from within, under conditions which warrant local treatment of the puncture wounds only, the remainder of the wound

being undisturbed. We need not elaborate upon this point for we are all aware that the cleanliness of the patient, the type of his clothing, the kind of bullet, the absence of injury to bones, tendons, nerves, *etc.*, are the principle determining factors. As an example we cite a Chinese war experience in which every bullet or knife entered the body encased in wool carried in from the soldier's uniform. Under such circumstances, it was necessary to lay such

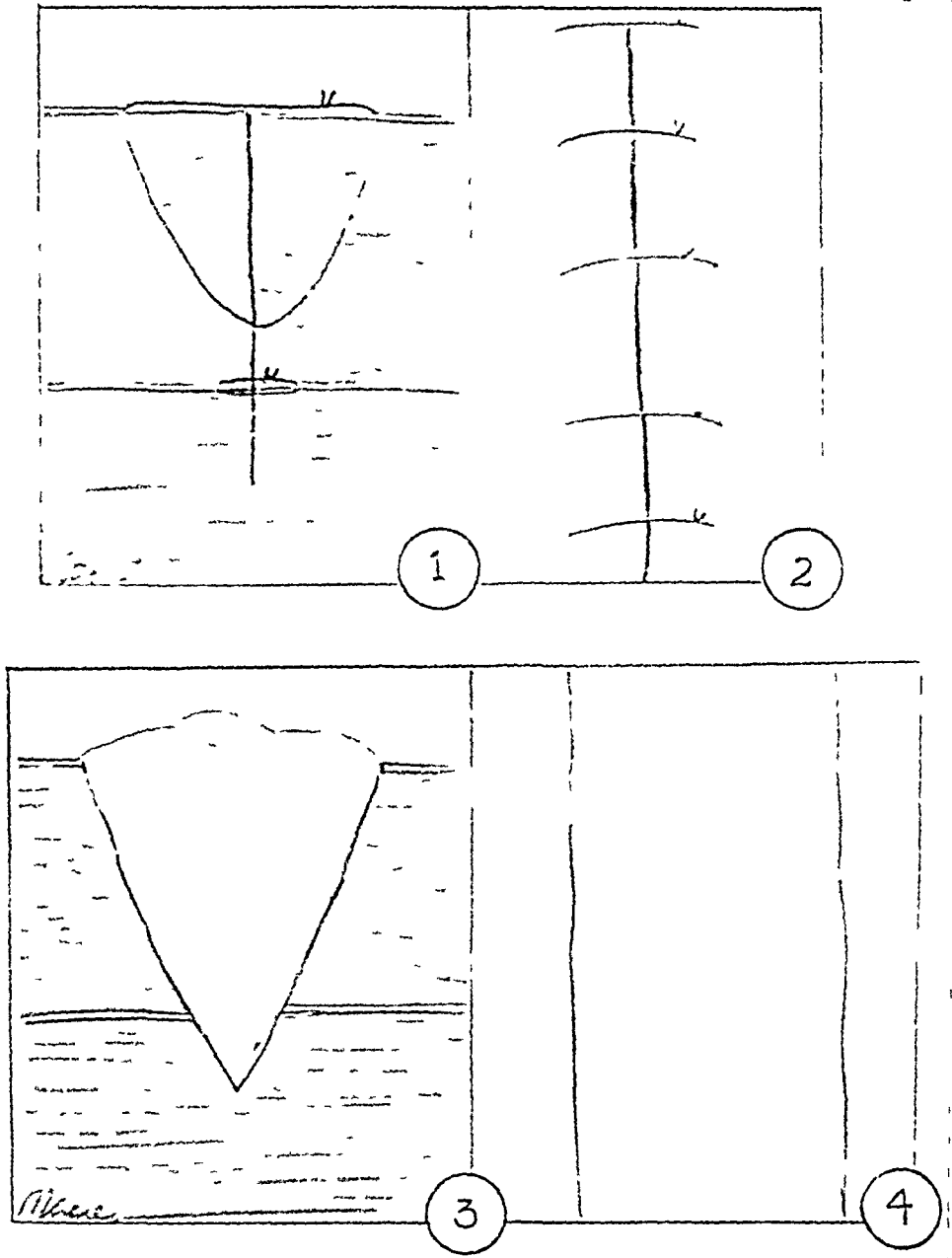


FIG. 4—(1) and (2) Primary closure of the wound. The fascia over the muscle has been sutured with silk. The skin sutures have been so placed as to leave as little dead space as possible. These sutures are placed rather far apart and tied loosely. (3) and (4) If primary closure is not feasible the wound is packed loosely with gauze. A plaster encasement is then snugly applied so as to completely immobilize the part.

wounds wide open to the very depth of their extent, to excise the tracks, and to remove all retained foreign bodies, which usually could not be recognized until the wool was removed from them.

When the simpler procedure is adopted, the cleansing of the skin, the draping of the wound, and the introduction of the anesthesia are done as already described. The smooth stab wounds are washed superficially with salt solution and closed without drainage. The gunshot wounds are excised through skin and fat, washed in this area with normal salt solution, as though they were to be closed, and then usually left unsutured. They are filled with vaseline, covered with vaselined gauze and immobilized in a dressing which is not disturbed until there is an indication for doing so.

(4) *The treatment of contaminated, lacerated and obviously traumatized wounds by debridement, cleansing and suture, or suture plus grafting, or grafting alone*

Such operations are preferably performed under a tourniquet which, because of pain caused by it, usually requires a general anesthetic. When the wound is of a serious nature or on a patient who has been brought out of shock, there is always on hand, in the operating room, intravenous fluids and blood before the operation is begun.

If pain is not a serious factor, the field of operation is prepared, as previously described, before the anesthetic is administered. If the injury is near the hand or foot, the part is scrubbed and the nails given the same meticulous care that the operator would give his own hands.

The purpose of the tourniquet is to save blood and to prevent unnecessary clamping of many bleeding points, which reduces the amount of ligature material in a wound and the time spent to put it there. The tourniquet maintains a clear dry field for the dissection and enables one to avoid soiling of freshly cleansed areas by the overflow of tissue juices and blood, or by frequent sponging of the field with gauze which will so easily touch both clean and dirty areas at the same time and also add unnecessary trauma.

No washing of the wound is done until the debridement is completed for this may not only obscure foreign bodies but will, under the influence of the tourniquet, make it far more difficult to differentiate between living healthy tissue and devitalized tissue which has not yet had time to change its color.

A dry sponge is tucked into the wound. An elliptical incision is made through normal skin about one-quarter inch from the edge in large wounds. This is carefully developed into the fat, but not through it. As the incision approaches the cavity, blood stains are observed in the tissue and its direction is changed. The clean skin flap is undermined as the edge is held up by small retractors. The undermining continues until the subcutaneous fat joins the muscle fascia. If there is doubt as to where this occurs, the clean wound is protected with moist flat gauze, the field protected with towels, the fluff removed from the dirty wound with a clamp and the cavity inspected. Another dry gauze is replaced and the clamp is kept in a separate basin for similar future use. In this manner, the entire wound is followed through the muscle fascia and torn muscle bellies. Long muscle fibers are split with a knife and incisions crossing the fibers are best made with small scissors. Areolar tissue

can be followed along periosteum, vessels, tendons, and nerves. The field and clean wound should always be protected with towels and moist gauze, so that in case of contamination the protection can be changed or removed, rather than covered over and allowed to remain as another source of unrecognized contamination.

Often the dirty wound and all devitalized tissue can literally be lifted out, *en masse*, without a serious break in technic. The wound is then washed with normal salt solution. Gloves and gowns are changed, clean instruments are secured and the field again redraped up to the edges of the incision, after another coating with tincture of mercuriolate which must not enter the wound. Before the tourniquet is removed any known or discoverable open vessels, which are sure to bleed, are ligated with fine black silk. The wound is packed with dry gauze which is held in place with decreasing firmness, for several minutes after the tourniquet is removed. This will stop many small bleeding vessels and make unnecessary the use of many ligatures which cannot help but add some necrosis to the wound. As this gauze pack is teased out, the other bleeders obviously requiring ligature are clamped and tied. Then, the oozing and smaller bleeding points, which one prefers not to tie, can usually be stopped by gentle pressure with warm (not hot) moist gauzes. Any overlooked pieces of ischemic tissue, revealed by the returning circulation, should now be carefully trimmed away. The wound is again washed with normal salt solution and closed throughout with fine silk or, if necessary, grafted. The wound is dressed with a dressing which secures complete immobilization and is not disturbed until all danger of manipulation from removing it is gone. If it is necessary to remove the skin sutures before one is ready to change the encasement this can be done through a window cut in the encasement. As will be noted later in this paper, it is felt very unwise to cut a window in an encasement covering a wound which has been packed with gauze. However, there seems no good reason for not doing so in the case of a wound which has been closed primarily or grafted, provided the window and dressings are replaced with their original degree of firmness.

Severed tendons and nerves, and compound fractures often give the most trouble in carrying out this ideal debridement, cleansing, and closure. In the latter cases, the dirty cavity is entered when the broken fragments are encountered. However, there need not be any contamination if one is careful to keep the clean surfaces covered. The soiled specimen is clipped free and discarded. The wound is next lengthened in either longitudinal direction until the end of either fragment can be brought out for further debridement. Soiled periosteum stripped from the bone must be sacrificed. It is at this state when the delayed washing of a wound is most appreciated. Dirt particles are now visible and there is no guesswork in their removal. With an osteotome, or thin chisel, a shaving of cortex is started from the clean portion and carried to the end of the soiled fragment. It is picked off with a clamp and discarded. The entire dirty area of bone denuded of periosteum is cleanly

shaved in this manner. The tip of the fragment, if dirty, is cut off with the same instrument or perhaps a saw or bone cutter. It is not advisable to use a rongeur for any part of the work. Its biting edges always pass through soiled surfaces, besides tending to leave partially detached pieces of bone.

When debridement of the fragment is completed, it is covered with gauze and returned to the wound. The end of the other fragment is lifted out and similarly treated. After this is done the extreme depths of the wound are systematically given debridement and the cavity is ready for irrigation. Large quantities of warm, but not hot, saline are used. While being irrigated, the wound is gently rubbed with a gloved finger to detach pieces of loose tissue and blood clots.

No mechanical fixation of bone fragments in the wound is employed. Tendons and nerves are sutured with silk. The wound is closed with interrupted sutures of silk. If the closure is under tension, and it usually is in fracture cases, counterincisions are made on either side to give relaxation. These defects may be skin grafted or packed with vaselined gauze and allowed to heal by second intention. Viability of skin over the fracture site depends on a closure without tension, the conversion of a compound fracture to a simple one depends on the skin remaining viable and intact. A moist gauze dressing is applied. The fragments are immobilized by skeletal fixation with pins or by an encasement alone, depending on the type of fracture, but they must be perfectly immobilized. The patient is given the usual prophylactic dose of tetanus and gas bacillus antisera. The dressing is not disturbed for weeks unless there is an unexplained rise in temperature or abnormal pain.

Let us here, again, call attention to the word "debridement" which has been defined as the "excision of a wound." The term has degenerated in its application. Almost any form of wound cleansing has been called debridement—and wrongly so. Most doctors know what it means, and start such operations with every intention of being thorough. The skin and fat receive fair treatment. Then, many of us will begin washing the wounds to take away every bit of the evidence of deep-seated dirt. The rest of the procedure will be devoted to aimless picking and clipping of tags of muscle and fascia over its surface. To be sure, the wound will look clean. One can wash the hematoma and extravasated blood from the muscles of a dressed rabbit which has been shot, but it will still be riddled with bird shot, hair and material from the intestinal tract. The operation does not terminate because the work has been systematically completed, but because patience has been exhausted and one does not see anything more that can be done.

The importance of this method of dealing with compound fractures prompts us to cite the following case as an example.

Case Report—T S, age 24, was admitted to the hospital, February 5, 1937, with a compound fracture of the left leg at its middle third. It had resulted from a pile of bricks falling on the extremity.

General examination was not remarkable. The leg presented a laceration, four

inches long at the site of the fracture. There was gross soiling of the wound. No history or evidence of bone protrusion could be obtained although the fractured ends were visible in the wound. Four hours after the accident the patient was operated upon under general anesthesia. Debridement was carried out as outlined above. Upon inspecting the bone gross dirt was found embedded in the periosteum at the point of fracture. It was removed according to the method described. Silk was used throughout. The closure was facilitated by accessory incisions which were later dressed with vaselined gauze. The leg was placed in a padded spica encasement and supported on a knee flexion-splint. Gas and tetanus bacilli antisera were administered and the patient returned to the ward in good condition.

The temperature curve showed spiking to 101° F during the first three postoperative days. It then dropped to normal for one day and spiked again on the fifth, sixth and seventh days. At this time there was evidence of a moderately severe serum rash. The elevated temperature and increased pulse were not accompanied by an increase in respirations. The temperature promptly subsided with the rash. All sutures were removed at the end of two weeks when the first dressing was made. The relaxing incisions were redressed and found to be nearly closed. The patient was discharged to the Fracture Clinic February 23, 1937 to be treated as if he had a simple fracture.

It appears also worth while for us to cite a case illustrative of the value of immediate skin grafting in the primary closure of traumatic wounds. As was done in this case many of these patients can be handled without admission as bed patients in the hospital.

Case Report—R. M., age 47, entered the hospital, February 12, 1938, following an injury of the right hand, sustained while cranking an automobile. The engine had "kicked," causing the end of the crank to tear through the dorsal surface of the web between the thumb and index finger. The skin and subcutaneous fat were missing. The extensor pollicis longus tendon was exposed, the adductor pollicis muscle was almost completely mangled, and there was a compound fracture of the first metacarpal bone at its middle third.

Three hours after the accident, debridement was begun, under local anesthesia, with the realization that skin grafting would have to be done in order to close the defect. However, a bridge of extensor pollicis longus tendon across the wound had not been anticipated. It would have been better to have covered the wound with a flap of skin and subcutaneous fat from the abdominal wall. However, the patient could not stay in



FIG 5—Primary skin graft to cover a tendon exposed through loss of overlying tissues by the injury. See report of case (Stevenson and Reid *Am Jour Surg*, 46, 442-449, December, 1939, Fig 3)

the hospital and, to simplify his care, a split-graft was removed from the thigh to cover the defect Six weeks later he returned to his job as pressman in a print shop

The photograph (Fig 5) shows a very superficial position of the tendon Although the graft is adherent to it, there is enough freedom in movement in other tissues beneath the graft to give the thumb a full range of function It is doubtful whether this tendon would have survived any delayed form of grafting The patient still refuses further correction

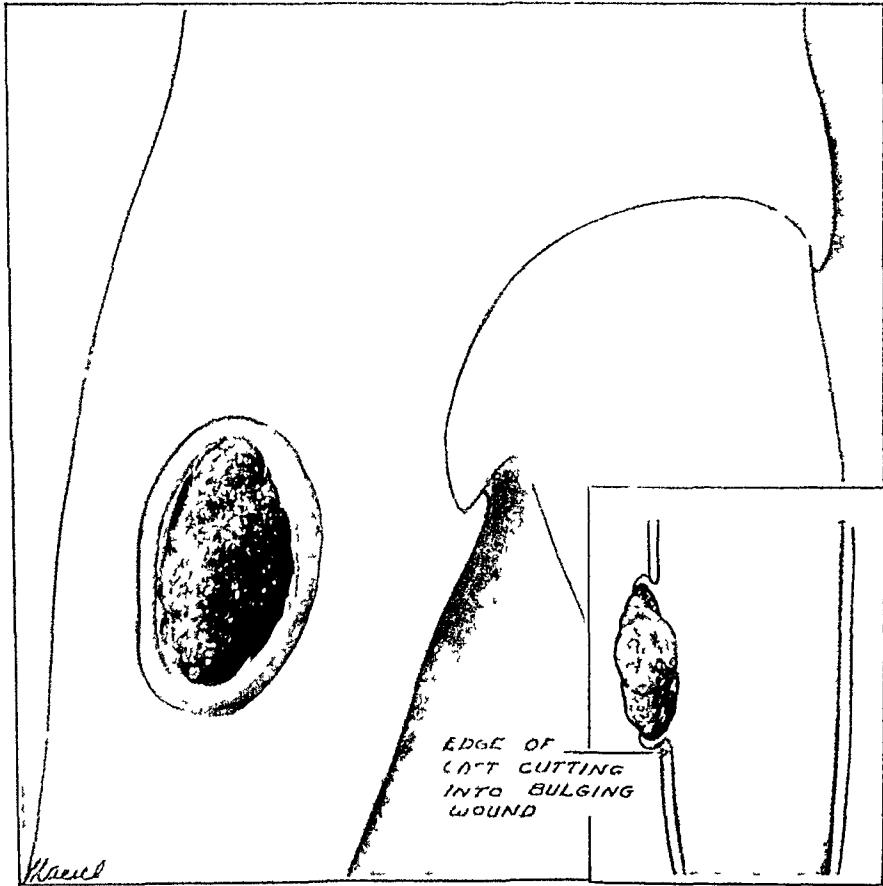


FIG 6—The effect on the underlying wound produced by cutting a window in the encasement over it The circulation in the wound is interfered with and its immobilization is destroyed

It should be stated, however, that serious cases such as we have been describing may, if the patient's condition demands it, be postponed for a day or possibly two, after the debridement and cleansing, for delayed primary suture

(5) *The treatment of traumatic infected wounds or contaminated wounds which, because of the exigencies of the situation such as often arise in war time, should have no attempt made at primary closure* In war, the facilities at one's command, the conditions under which one has to work, and the lack of trained personnel often make it very unwise to attempt any primary closure of traumatic wounds This was invariably the case in the Chinese war to which we have referred

While most surgeons adopt an arbitrary time limit of six to eight hours in deciding whether a wound is contaminated or infected, we are influenced by the nature of the soiling, the location and extent of the injury. For instance, we all know that we can take more chances that wounds about the head and face are only contaminated, even though they have exceeded our adopted time limits. On the other hand we know that it was very unwise to gamble with contamination versus infection when the soiling was from Flanders fields or the trenches. When in doubt smears from the tissue pieces might show large numbers of bacteria and thus throw the decision in favor of infection. However this section of our paper deals only with the preparation of fresh wounds usually not over three days old, for healing by secondary intention, secondary closure or skin grafting. Tetanus and gas bacillus antitoxin are always administered to such patients.

The field of operation is prepared as already described. A general anesthetic is much preferred. A tourniquet is used if possible. The wound is laid extraordinarily wide-open so that no packs, drains or tubes will be regarded as necessary. Foreign bodies and completely detached pieces of bone are removed and all recognizable dead or devitalized tissue cut away. It cannot be overemphasized that the success of this method is directly dependent upon the thoroughness of the debridement. Grease- and dirt-stained living tissues particularly bone, tendons and nerves, are completely cleansed with soap and water using a scrub brush if necessary. This is followed by a most thorough washing with normal salt solution using the gloved finger to massage the tissues gently. Following this, gowns, gloves and instruments are changed, the skin is dried and recoated with merthiolate, new drapings are applied. The tourniquet is removed and bleeding vessels are ligated with very fine chromic catgut ligatures. Tendons and nerves are not sutured, there is no internal fixation of fractured bones. The wound is not even partially closed. It is filled with vaseline or with well-saturated vaselined gauze, or with both and then so dressed as to be as absolutely immobile as it is possible to make it. The pressure of the dressing over the wound is made quite firm in order to combat the tendency toward edema in it. If possible, such a dressing is left undisturbed until the protection of a healthy granulation tissue is formed, or until the dangers of manipulation from removing the dressings are negligible. This usually means two weeks and may mean more than four weeks. Above all, we try to avoid dressing such a wound through a hole in an encasement which, because of the lessened pressure, will often allow the wound to become edematous and actually herniate through the encasement. This has always appeared to us to be a serious handicap to the healing of such a wound. We prefer, when the dressing has to be made, to remove the entire dressing and replace it with a new one.

Healthy and unharmed granulation tissue is such a good protection that we can see no reason for disturbing it until the time arrives when we wish to prepare it for secondary closure or skin grafting. This may be early or late, depending upon many circumstances, such as the complications of frac-

tures or osteomyelitis in the wound, or such as the equipment and personnel at the disposal of the surgeon. For such preparation of granulating wounds we prefer to use Dakin's solution, but that is another story which is beyond the scope of this paper.

Those of you who heard Doctor Matas at our meeting last year, or have read Winnett Orr's paper or J. Trueta's book, will recognize a familiar tone throughout this paper. Doctor Matas' description of the management of the war wounds in the Spanish Civil War was truly delightful. We want to close this paper with two quotations from the remarks he made at that time. The first is "There, at the war front, rude experience imposed by necessity seemed to discount the importance of germs, provided the living tissues were allowed to fight their own battle unencumbered by the bodies of dead or dying tissues, and kept undisturbed and protected in the process of repair and reproduction from tempestuous manipulations and destructive germicidal irrigations by absolute fixation in plaster." The second is "Suffice it to say, that when fresh wounds are relieved of all dead or devitalized tissues, they are, when put to complete rest, quite able to take care of themselves without the aid of antiseptics, which (when truly bactericidal) hinder the normal reproduction of the tissue cells and weaken their defenses."

This paper was read before the Fifty-third Annual Session of the Southern Surgical Association, Hot Springs, Va., December 10, 11, 12, 1940.

THE USE OF SULFANYLGUANIDINE IN SURGICAL PATIENTS

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IN SEPTEMBER 1940, Marshall and his coworkers published the results of their studies with sulfanylguanidine.¹ Their paper described the method of preparation and the properties of this compound. They reported careful experiments on mice, rabbits and dogs which were designed to compare the relative toxicity of sulfanylguanidine with sulfapyridine and sulfathiazole. From these experiments it appears that this new sulfonamide compound, when given orally, is probably less toxic than sulfapyridine or sulfathiazole. The investigations of Marshall and his group brought out clearly two facts of possible significance for surgeons. They showed that, although sulfanylguanidine is fairly soluble in water, it is poorly absorbed from the intestinal tract, and secondly, that the concentration of coliform bacteria in the feces of mice is greatly reduced after the oral administration of the drug. Furthermore, they found that the new compound is as active as sulfapyridine is against pneumococcus infections in mice, and from studies *in vitro* they showed that it is as effective as sulfanilamide is against several other pathogenic bacteria.

It was these observations that led us to consider using sulfanylguanidine in the preparation of patients who needed operations upon the colon. The present paper is an account of our experience with this drug in 12 such cases.²

CASE REPORTS

Case 1—H. G. The first surgical patient upon whom sulfanylguanidine was used had had a long and tedious experience with previous operations. She was age 39 when admitted to the Johns Hopkins Hospital. Eighteen years before a cyst had been removed from the left ovary. Seven years later an exploratory celiotomy was performed for partial intestinal obstruction. Three years thereafter a second cyst was removed from the left ovary. For the following seven years the patient had been comfortable but, then, periods of cramplike pain in the lower abdomen recurred. The persistence and severity of these attacks increased and became associated with distention, nausea and vomiting. Such was the account given by the patient of her illness, and efforts to obtain actual data bearing on the previous operations were of no avail.

The patient was admitted to the Gynecologic Service. The physical examination failed to reveal any deviation from the normal, except in the pelvic organs which were embedded in moderately firm adhesions. Several loops of intestine were thought to be attached to the left adnexae. With the patient under anesthesia, a mass was felt which was adherent to the left uterine cornu, and fixed to the left lateral wall of the pelvis.

Operative Note—The abdomen was opened through a low midline incision. Part of the omentum formed a mass which was attached to the left side of the uterus and to a large ovarian cyst that was adherent to the left pelvic wall. After some dissection, it was found that the right tube and ovary were missing. A supravaginal hysterectomy was then completed, and it became evident that the left tube and a loop of intestine were

* The sulfanylguanidine used in these studies was supplied by the Calco Chemical Company.

firmly attached to the ovarian cyst. Considerable bleeding was occasioned by the removal of these structures, upon completion of which the operator found a peculiarly narrow strip of intestine, which was devoid of mesentery, extending from the descending colon to the rectum. This loop of bowel was approximately eight inches long and, unfortunately, was open in two places. After considerable dissection, it became clear that the sigmoid had been removed previously, and that a segment of ileum had been interpolated to connect the descending colon and the rectum (Fig 1). This nonviable,

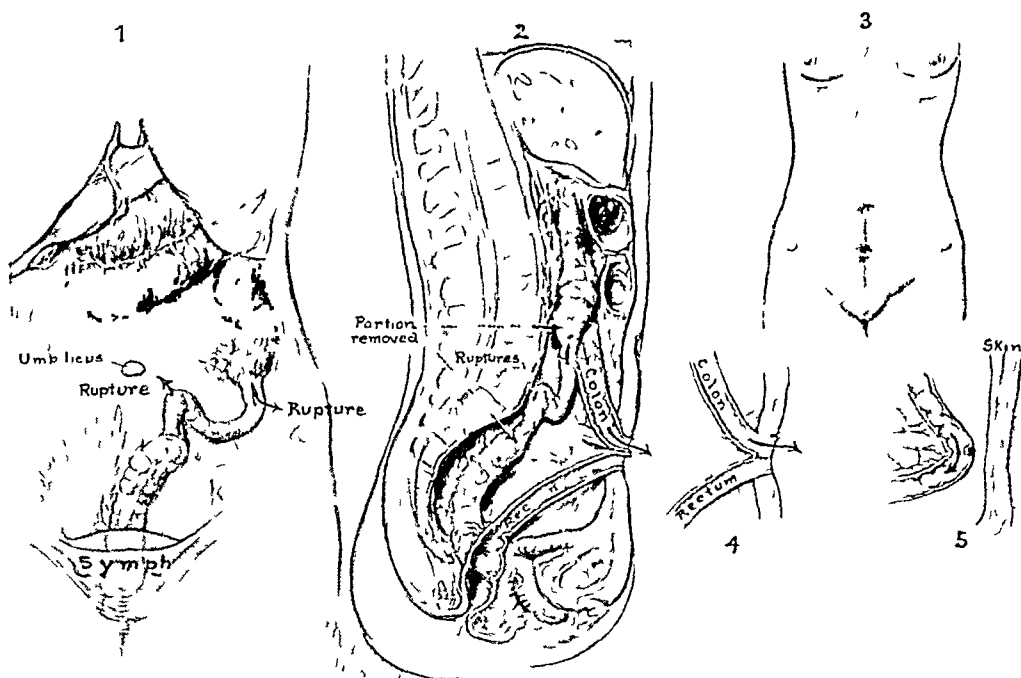


FIG 1—Case 1. Drawings illustrating the conditions present in this patient.

perforated loop of bowel was then resected, the end of the descending colon freed from adhesions and opened, and the upper end of the rectum mobilized and opened. The patient was showing the effects of the long operative procedure, and, as there had been considerable fecal contamination, the operator felt that an end-to-end anastomosis was out of the question. The open ends of the colon and rectum were then brought through the midline incision, and the wound closed above and below the openings. There was so little tissue available that a very short spur resulted from the approximation of the descending colon with the rectum.

The spur was subsequently removed and an effort made to close the colostomy with sutures. The tension between the loops was too great, and the wound broke open. At this point in the patient's convalescence she was given 7.5 Gm of sulfanilylguanidine by mouth every day for one week. The concentration of coliform bacteria in the colonic discharge fell rapidly, and a second operative closure was attempted. At this operation the open ends of the colon and rectum were dissected from the abdominal wall, freed from adhesions and lengthened. The proximal and distal ends were joined by two layers of sutures. In carrying out this anastomosis there was gross soiling. The sutured bowel was replaced in the peritoneal cavity, and the abdominal wound closed with silk without drainage.

Only twice after the operation did the patient's temperature go as high as 100° F. On the fifth postoperative day she began to have normal stools and, except for cramp-like pain, her convalescence was uneventful. There was one very small stitch abscess which

cleared up in 24 hours after it was opened. The patient continued to receive sulfanilylguanidine every day for a week following the operation.

SUMMARY—A patient, who after several previous operations, required a colostomy of the Mikulicz type, in which the afferent and the efferent loops were under tension. The colostomy was successfully closed and the bowel placed intraperitoneally despite gross fecal contamination.

Case 2—C. M. This vigorous, middle-aged white male, came to Johns Hopkins to have a colostomy closed. He gave the following account of his illness. On March 12, 1940, he was awakened by pain in the lower part of the abdomen. The intensity of the pain rapidly increased and was followed by nausea, vomiting, and fever. He was unable to work, which was most unusual for him. His family physician felt that an operation was imperative, and 18 hours after the onset of his symptoms a celiotomy was performed through a midline incision. The peritoneal cavity was found to be full of "milky fluid." There was a mass arising in the sigmoid. The segment of diseased bowel was removed. The patient was told that the lower end of the sigmoid adjoining the rectum had been closed and placed in the pelvis, and that the proximal end of the divided bowel had been brought through the abdominal wall in a separate incision (left pararectus). Subsequently the terminal end of the descending colon either retracted to form an abscess or became gangrenous. The patient only knows that the wound was badly infected, and that a second operation was required in order to have the colostomy function.

On admission he was seen to be an obese man in no apparent ill health. On examination the rectum was found to extend five inches above the internal sphincter. The colostomy opening was small and was surrounded by a broad area of dense scar tissue. The patient was given 4 Gm. of sulfanilylguanidine orally every eight hours for six days. A solution of the drug was used on three occasions as a retention enema to reduce the bacterial count in the rectum. At operation innumerable adhesions were encountered beneath both incisions (Fig. 2). The ends of the divided bowel were mobilized and the terminal portions excised to facilitate anastomosis. It was found that a sizable portion of the descending colon and most of the sigmoid were missing. The operator was forced to mobilize the hepatic flexure in order to obtain approximation of the colon to the rectum. In doing this the tension was so great that the colon was stretched and flattened, consequently a six-inch rubber tube one inch in diameter was placed in the lumen of the bowel and an anastomosis made around this tube. Interrupted sutures of catgut were used and wherever possible these were reinforced with Lembert sutures of silk. One could not be certain that the anastomosis was secure at any point. A Penrose wick was placed in the midline wound, and both incisions were closed with silk throughout. The cecum was then brought through a right McBurney incision with the expectation that it would be subsequently opened.

For nine days after this operation the patient received 4 Gm. of sulfanilylguanidine orally every eight hours. There was never any distention, there was no leakage from the anastomosis, and there was prompt and frequent passage of flatus and feces per rectum. On the ninth day after operation the patient strained and passed per rectum the large rubber tube that had been supporting the line of anastomosis. Previously the lower end of this tube had been barely palpable by digital examination. The complete absence of distention made the opening of the cecostomy quite unnecessary. Both abdominal wounds healed promptly without infection. Following the operation the patient's temperature only once was above 100° F., and was entirely normal after the fourth postoperative day. His pulse rate ranged between 90 and 100 for three days and thereafter was in the 80's. He left the hospital three weeks after the operation.

SUMMARY—Previously a resection of part of the descending colon and most of the sigmoid had been performed. The distal end of the sigmoid had

been replaced in the pelvis. An open tube anastomosis was carried out, restoring the continuity of the large bowel. The anastomosis healed *per primam*.

Case 3—W. B. A white male, age 73, who had been treated previously in the Johns Hopkins Hospital for generalized arteriosclerosis, arteriosclerotic heart disease and hypertension, was readmitted, complaining of a gastro-intestinal upset. Upon questioning it was found that three months before he began to experience gastric pain an hour and one-half after meals. The pain persisted until the following meal. In addition he had had cramps in the lower bowel which sometimes awakened him. The bowel move-

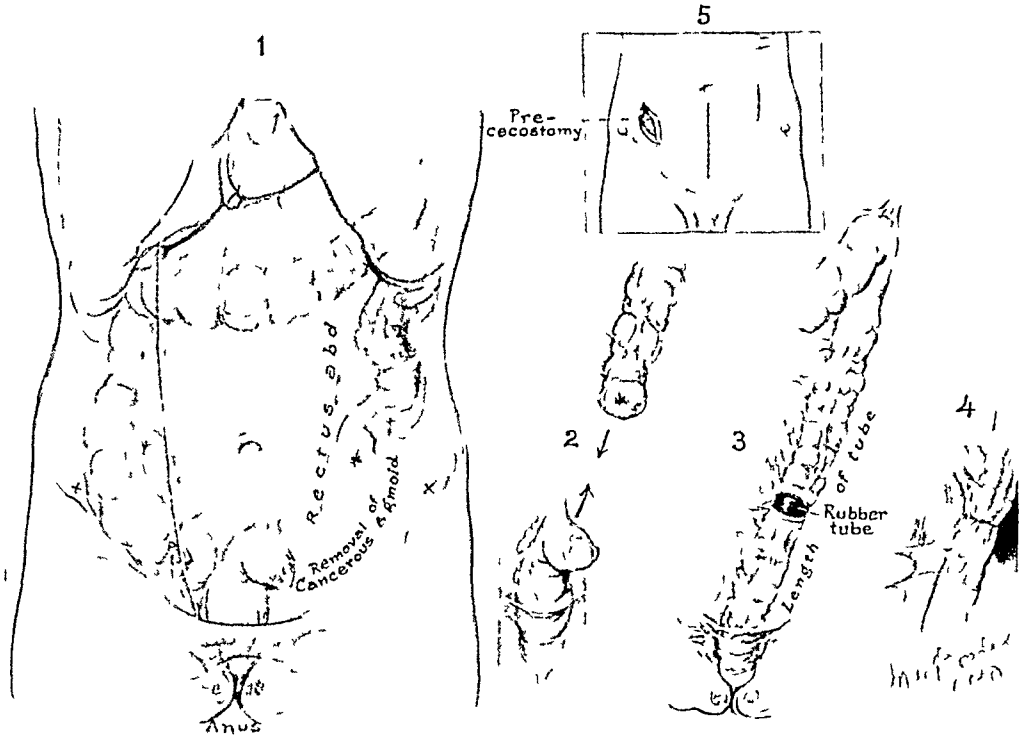


FIG. 2—Case 2. Drawings illustrating the conditions present in this patient.

ments had become watery and loose, and at times his stools had been dark. The patient had tried various diets without any success. One week before coming into the hospital he had two short attacks of pain radiating along the course of the right ureter. He described the pain as intense, otherwise his history was unessential. On physical examination, there were obvious evidences of arteriosclerosis, the heart was enlarged to the left, there was a precordial systolic murmur, and tenderness on palpation in the lower part of the right side of the abdomen. His blood pressure was 210/110. He was thoroughly studied on the Medical Service. A barium enema showed a persistent filling defect in the ascending colon below the hepatic flexure. The characteristics of the defect strongly suggested the diagnosis of malignancy. There was also evidence of adhesions around the cecum.

Upon questioning, the patient gave the additional information which proved to be of the utmost importance. Forty-three years before, while on a bicycle trip through France, he had an attack of acute appendicitis. An appendiceal abscess formed and ruptured into the cecum. No operation was performed. The patient had had no subsequent indication of infection in this region.

He was given 4 Gm of sulfamylguanidine by mouth every eight hours. On the fourth day the patient became drowsy and cyanotic. He was thought to be showing signs

of toxicity, like those seen in sulfanilamide poisoning. The daily blood levels of combined sulfanylguanidine had been running between 4 and 4.5 mg per cent. At the time of his drowsiness the blood level was found to be 23.6 mg per cent. Investigation showed that the patient had been given 24 Gm of sulfanilamide by mistake. This drug was obtained from his urine, and analyzed by E. K. Marshall, Jr. The patient continued to receive sulfanylguanidine following the error, and daily blood level determinations showed after 48 hours that the concentration of sulfanylguanidine had returned to 4.5 mg per cent.

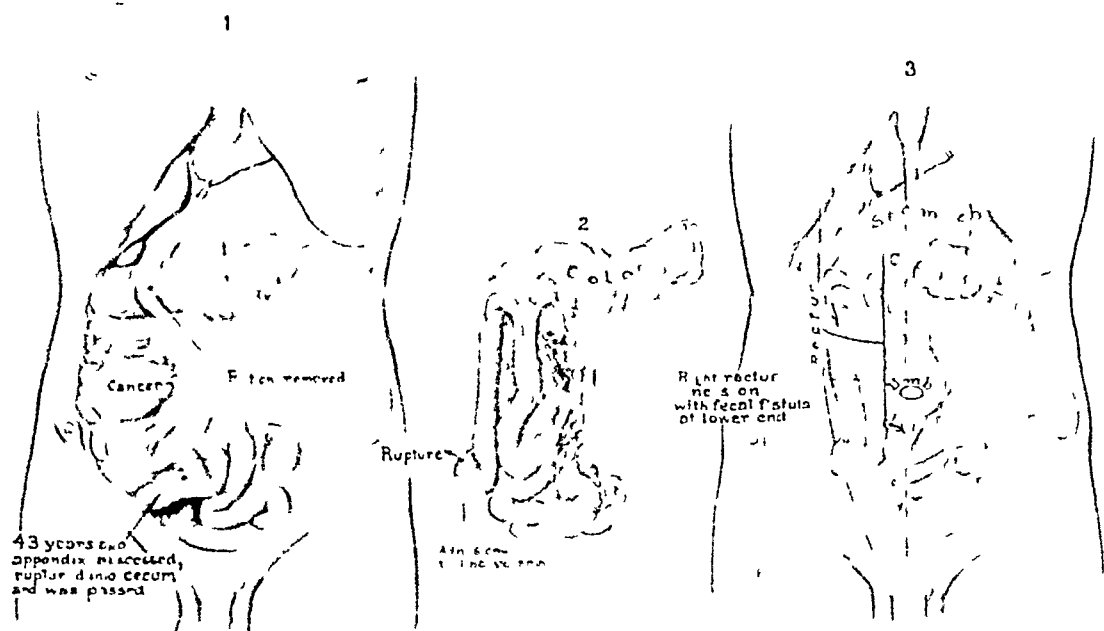


FIG. 3.—Case 3. Drawings illustrating conditions present in this patient.

After seven days of preparation by chemotherapeutic agents he was operated upon. There was a large carcinoma just below the hepatic flexure which was fixed to the parietal peritoneum. The nodes in the mesentery were enlarged and firm. There were many short, tough adhesions at the site of the appendiceal abscess. The terminal ileum and its mesentery were closely attached to the common iliac vessels (Fig. 3). The operator divided the terminal ileum about 2 cm from the ileocecal valve, and resected the right side of the colon, removing the tumor and the mesentery. The patient's cardiovascular condition was not particularly good at any time, and it was a question whether to attempt to dissect the terminal ileum from its attachment to the common iliac vessels, or to invert the stump and establish a lateral anastomosis between the ileum and the transverse colon. The removal of the tumor had been tedious and the dissection had been difficult. It seemed wise, therefore, to shorten the time of operation as much as possible, consequently, the end of the transverse colon was sutured to the ileum about 18 cm above the inverted end of the terminal ileum. The wound was closed with silk throughout. No drains were used.

For five days after the operation the patient did surprisingly well. Only once did his temperature go above 100° F, and within 48 hours after the operation his temperature was normal and remained so. His pulse rate varied between 88 and 104. There was some distention, but he had bowel movements. On the sixth day the lower angle of the incision opened, discharging both gas and fecal matter. It seemed clear that the sutured end of the terminal ileum had opened and that a fecal fistula had developed. A very surprising feature in this case is that the patient had given no signs of peritonitis. He had no abdominal pain or tenderness. There was no fever or tachycardia and, although the

wound had been closed tightly, the lower angle opened spontaneously to accommodate the discharge from the terminal ileum

During the five days after the operation he had continued to receive 12 Gm of sulfamylguanidine by mouth each day. When the fecal fistula developed, he was given sulfathiazole intravenously and later by mouth. His subsequent course is uneventful except for the development of an abscess which opened through the upper angle of the wound. The fistula is closing slowly at the present time*.

SUMMARY—Carcinoma of the ascending colon in an elderly patient suffering from arteriosclerotic heart disease and hypertension. Forty-three years before, an appendiceal abscess had spontaneously ruptured into the cecum. A right-sided resection was carried out with an ileotransverse colostomy. A fecal fistula developed from the terminal ileum.

Case 4—L. D. An obese white female, age 57, came reluctantly to the Johns Hopkins Hospital. Her previous experience with surgery elsewhere had been most discouraging. In July, 1936, after months of discomfort, she was operated upon for hemorrhoids and "inflammation" of the cervix. Following this she complained of indigestion, eructation and weakness. In October of the same year, a second operation was carried out. The patient was told that the appendix was diseased and had had to be removed. Furthermore, adhesions around the gallbladder had been freed and a dermoid cyst involving the left ovary and colon necessitated an oophorectomy and a partial colectomy. After the operation the patient found herself with two incisions—a low midline one and a high left rectus one, through each of which the divided end of a loop of colon protruded. Her convalescence was uncomfortable, a purulent discharge from the rectum was present which required irrigations through the lower colostomy. Fever and attacks of pain continued for five months, terminating promptly when a gauze sponge was extruded from the left rectus incision. This necessitated a plastic operation to insure proper function of the colostomy. For 18 months the patient was free from symptoms, and then she had the first of seven attacks of acute intestinal obstruction. Each attack was relieved by good nursing care. The last obstruction was so obstinate, however, that she was forced to seek surgical aid.

On examination, one found that the patient had two abdominal scars (Fig. 4) each of which marked the site of a large ventral hernia containing many loops of small intestine. The distal end of the severed colon had retracted beneath the low midline scar and was completely closed, the proximal end of the colostomy was functioning.

The patient was given sulfamylguanidine orally 4 Gm. every eight hours for eight days, together with a low residue diet and daily enemata through the colostomy.

At operation, there were, of course, extensive adhesions between the loops of intestine, both in the hernial sacs and in the abdominal cavity. The disparity in the caliber of the proximal and distal ends of the colon was so great that an end-to-end anastomosis seemed inadvisable. The continuity of the colon was reestablished, therefore, by a lateral anastomosis. This was carried out by the open technique and, despite the preoperative enemata, fecal matter was extruded during the operation. When the anastomosis was complete, the colon was placed within the peritoneal cavity, a Penrose drain was put in the lower angle of the midline incision, and both wounds were closed with silk throughout. The operation took over three hours, but a transfusion and the administration of fluids intravenously prevented any detectable evidence of shock.

On the day of operation, the patient was given 4 Gm. of sodium sulfathiazole intravenously and 4 Gm. of the same drug by mouth. The following day she was given 12 Gm. of sulfamylguanidine, but an extensive macular rash developed over the entire body. It was thought that this was the result of sulfathiazole, and for 24 hours the

* Two weeks after the meeting of the Southern Surgical Association this patient contracted bronchopneumonia and passed away.

drug therapy was suspended. The rash persisted and in order to eliminate sulfamylguanidine as a causative agent, this drug was resumed in the same dosage as before, and continued for eight days during which time the rash completely disappeared. The patient's convalescence was noteworthy for the absence of distention and for the prompt and perfect healing of both wounds. She was discharged 15 days after the operation.

SUMMARY—Previous resection of part of the descending colon with double colostomy. Two ventral herniae were repaired with silk and the continuity of the colon restored by an open anastomosis. Healing *per primam*.

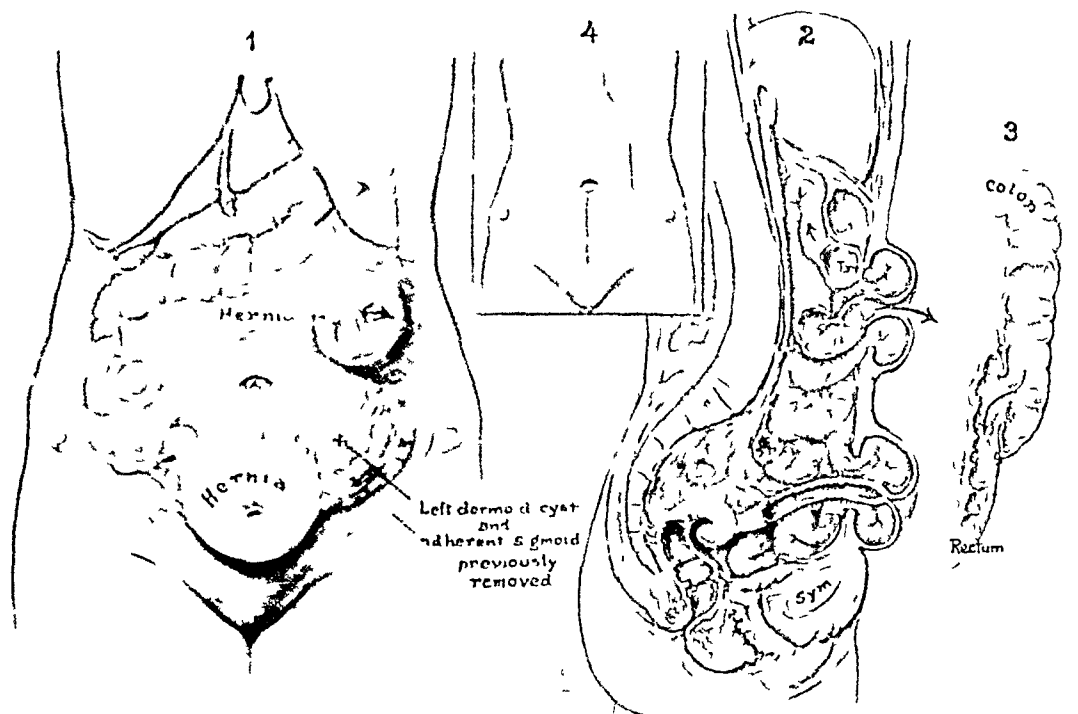


FIG. 4.—Case 4. Drawings illustrating conditions present in this patient.

Case 5—D. T. This emaciated white female, age 66, was a patient of Dr. Harvey Stone. She had had a long-standing illness of ulcerative colitis, for which an ileosigmoidostomy had been performed three years before the present admission. This operation was followed by a period of relative well-being, but for the last six months she had complained of diarrhea, chills, fever, malaise, and had lost 20 pounds in weight. When admitted to the hospital she was obviously acutely ill. During the first week of residence there her temperature varied from 98° to 102° F., her pulse rate from 100 to 130, and her blood pressure was 100/40. There was a large tender mass in the lower part of the left side of the abdomen. Sulfamylguanidine was given in doses of 3.3 Gm. every eight hours for ten days before operation.

A left rectus incision was made, and in an effort to mobilize the mass that had been palpated the operator broke into several abscess cavities. The transverse and part of the descending colon had become gangrenous and had perforated in at least three places. There was a gastocolic fistula. The walls of the stomach were so edematous that the closure of this fistula was unsatisfactory. The operator was finally able to deliver the gangrenous portion of the colon and to establish a Mikulicz colostomy. A drain was placed through a stab wound in the lower part of the abdomen. Throughout the operation the patient's condition was precarious, and two transfusions and intravenous fluids had to be given; the following day a third transfusion was needed. At this time it was noted that the urinary output was greatly diminished. There were casts which had not been present before. Three days after the operation the patient became

jaundiced and continued to have a meager urinary output. The progress notes recorded each day the absence of distention. There were no signs of generalized peritonitis, and by the third day after operation the pulse rate had fallen to 100 and the temperature to 99.8° F. Only once during the week after operation did the patient's temperature rise above 101° F. During the second week of convalescence she had a chill and fever after the intravenous administration of glucose solution. The renal function gradually returned to normal and her convalescence continued satisfactorily.

SUMMARY—Resection of gangrenous colon. Closure of a gastocolic fistula in the presence of abscesses without developing a generalized peritonitis.

The preceding cases were complicated ones that required detailed description. We have used sulfamylguanidine in seven additional patients whose histories are briefly abstracted in the following paragraphs.

Case 6—L. C. An obese colored female, age 58, came to the hospital complaining of constipation and blood in the stool. The past history was noncontributory. The illness that brought her to the hospital began two months before admission, at which time she passed a large amount of bright red blood per rectum. For the following week she had diarrhea, each stool containing blood and mucus. Thereafter she had alternately diarrhea or constipation, marked tenesmus, and discomfort in the lower abdomen. There had been no loss of weight. The physical examination was negative. There were no evidences of intestinal obstruction. A barium enema, however, showed a large filling defect in the lower portion of the descending colon. The patient was given 7.5 Gm of sulfamylguanidine a day for nine days before the operation was performed. An annular carcinoma of the sigmoid with metastasis to the regional nodes was found. This was removed, and an end-to-end anastomosis, with an aseptic technic, was carried out. At the same time a cecostomy was established. Following the operation she was given sulfamylguanidine for a week. Her convalescence was uneventful, except for a moderate degree of fever which persisted for six days. At no time, however, did her temperature go over 101.6° F. The cecostomy closed spontaneously. She had effectual enemata from the third postoperative day and normal spontaneous bowel movements after the seventh day.

SUMMARY—Annular carcinoma of the descending colon in an obese, colored female. An aseptic end-to-end anastomosis was performed. Healing *per primam*.

Case 7—E. D. A white male, age 19, had survived a severe automobile injury 18 months before admission to the hospital. At the time of the accident he suffered a fracture of several ribs and a left hemothorax. The patient gradually recovered, but six months later developed increasingly severe signs of partial intestinal obstruction. At the time of admission he was greatly distended. He had lost 60 pounds in weight, and was having constant cramplike pain and vomiting. A barium enema showed a definite obstruction at the splenic flexure of the colon. The abdominal cavity was opened and an enormous dilatation of the transverse colon, terminating in a benign stricture at the splenic flexure, was found; accordingly, a cecostomy for decompression was made. Two weeks later he was again operated upon, and the left half of the transverse colon, the stricture, and a portion of the descending colon were resected. The walls of the transverse colon were so edematous and friable that it appeared unlikely they could hold sutures; consequently, the proximal and distal segments were brought out on the abdominal wall side-by-side, in the manner of a Mikulicz resection. The disparity in the caliber of these two ends was striking, the proximal loop being three times as large as the distal one. After the clamps had come off, the larger segment gradually shrank in size, but even after the spur had been crushed the colostomy did not close. It became evident that operative measures would be necessary in order to close the colostomy. In preparation for the operation the patient was given sul-

familylguanidine. He received seven doses of 4.5 Gm at 12-hour intervals. At operation it was necessary to open the peritoneal cavity in order to mobilize the proximal and distal ends of the colon. The anastomosis was carried out in the presence of gross fecal contamination, nevertheless, no evidence of peritonitis appeared. The wound healed promptly and completely, except for a very tiny fistula that subsequently closed. Beginning 24 hours after the operation, the patient was given 4.5 Gm of sulfanylylguanidine by mouth every 12 hours for four days.

SUMMARY—A posttraumatic stricture of the splenic flexure, requiring resection and secondary colostomy, closure necessitating intraperitoneal suturing in the presence of feces.

Case 8—I S. This patient was a colored female, age 49, who was admitted to the hospital with a story that suggested the presence of a carcinoma of the sigmoid. The physical examination and barium studies confirmed this impression. She was prepared by the usual colonic regimen and by the administration of sulfanylylguanidine. She received 12 Gm by mouth daily for five days. At operation a large carcinoma of the sigmoid involving also an adjacent loop of ileum was found. The entire tumor and adjacent sigmoid, together with the segment of ileum, were removed in one piece. An end-to-end aseptic anastomosis of the sigmoid and a lateral open anastomosis of the ileum were then performed. The abdominal wound was closed without drainage. A prececostomy was provided, but was never opened. The patient had a smooth convalescence, her temperature reaching 100.4° F on only one occasion. The drug was continued for nine days after the operation, during which time the patient was entirely free from distention. Her wound healed *per primam*, and she left the hospital on the fifteenth postoperative day.

SUMMARY—Carcinoma of the sigmoid involving the ileum. Block resection of sigmoid and ileum with aseptic anastomoses.

Case 9—V S. A colored male, age 25, came into the hospital with symptoms and signs of acute appendicitis. At operation, the appendix was thought to be inflamed and was removed. Further exploration showed that the sigmoid and two separate areas in the ileum were involved by acute regional enteritis. Preparation had not been made for resection, and the patient's condition became so precarious that the abdomen was closed without further intervention. He ran a febrile course for two weeks following the operation. He complained of abdominal tenderness and cramplike pains. The wound drained small amounts of seropurulent fluid but never any fecal material. He was then prepared by the use of sulfanylylguanidine (9 Gm daily for four days), and a resection of the terminal three feet of ileum and the right side of the colon was carried out. During this operation a small abscess beneath the cecum was opened. An end-to-side ileotransverse colostomy was performed, by an aseptic technic, and the wound closed tightly with silk. The patient made a smooth recovery, his temperature never rising over 100° F. The drug was continued for a week after the operation. The abdominal wound healed quickly without the slightest evidence of infection.

SUMMARY—Regional enteritis involving three segments of the intestinal tract. Resection and anastomosis in the presence of a small abscess.

Case 10—V T. A colored male, age 32, complained of frequency and dysuria. He had lost 25 pounds in six months. The physical examination showed a large, poorly defined mass in the right iliac fossa. A barium enema brought out displacement of the rectum toward the left. While on the ward the patient developed progressive distention and intermittent abdominal pain. He was given sulfanylylguanidine (12 Gm daily for five days). At operation, he was found to have a large extraperitoneal tumor in the right side of the pelvis. Numerous loops of ileum were densely adherent to the tumor, and there was marked dilatation of the intestine above the adhesions. Attempts to free

the intestine were unsuccessful. The distention was relieved by performing an ileosigmoidostomy, with the open technic. The wound was closed with silk, without drainage. The postoperative course was remarkably smooth. The patient was discharged on the fifteenth day, his wound entirely healed, and his obstruction relieved.

SUMMARY—Intestinal obstruction caused by a large retroperitoneal tumor, probably sarcoma. Open anastomosis between the ileum and the sigmoid.

Case 11—I D. A white female, age 59, came into the hospital with symptoms that indicated she was suffering from a carcinoma of the transverse colon. The physical examination was consistent with this diagnosis. She was prepared for operation by the usual colonic regimen, and was given sulfanilylguanidine (7.5 Gm daily for six days). At operation, a large carcinoma of the transverse colon was found. This was densely adherent to the cecum. Resection from the terminal ileum to the left side of the transverse colon was performed, and an end-to-side ileotransverse colostomy carried out by an aseptic technic. Her course was smooth for eight days. She then developed fever (103° F), without corresponding elevation of the pulse rate. There was localized tenderness in the left lower quadrant, but no evidence of peritoneal irritation. Her temperature gradually returned to normal, the abdominal tenderness disappeared, the wound healed *per primam*, and she had daily numerous bowel movements, the same trend of events repeated itself on the thirteenth and twenty-fourth postoperative days. No mass ever developed, and the highly localized character of the tenderness suggested an inflamed diverticulum of the sigmoid. There was never any tenderness in the upper abdomen at the site of the ileocolostomy, and never any evidence of generalized peritonitis.

SUMMARY—Carcinoma of the transverse colon necessitating extensive resection and end-to-side anastomosis. *Per primam* wound healing and satisfactory bowel function. Three spells of fever and abdominal tenderness, probably due to diverticulitis.*

Case 12—S M. A white male, age 26, complained of abdominal pain, diarrhea, and blood in the stools. Barium studies showed an irregular filling defect in the cecum. The patient was prepared in the usual manner for a colonic resection, and was given sulfanilylguanidine for three days preoperatively. At operation, a number of polyps were found in the cecum. The right side of the colon was resected, and a lateral ileotransverse colostomy performed, by the open technic. The drug was continued for six days after the operation. The patient's convalescence was smooth. His temperature did not rise above 100° F at any time. The wound healed *per primam*. He was transferred on the fifteenth day to the Medical Service for the study of a microcytic anemia.

SUMMARY—Polyposis of the cecum. Resection of the right side of the colon, with open lateral anastomosis.

In each of the foregoing patients, determinations were made in Marshall's laboratory to ascertain the concentration of sulfanilylguanidine in the blood. More than 90 determinations were made with average total values of from 2 to 4 mg per cent. In only two instances was the total blood level as high as 5.0 mg per cent.

Similarly, in all the patients the concentration of coliform bacteria in the stool was studied before and after the administration of sulfanilylguanidine. This was done by making an emulsion of 1 cc of stool with 9 cc of P D broth. Serial dilutions in the ratio of 1:9 were made from this emulsion. One-tenth of a cubic centimeter of each mixture was added to a tube of desoxycholate agar and poured into sterile Petri dishes. After 48 hours' incubation at 37° C, the

* Subsequently, this was confirmed at operation.

number of colonies in each plate was counted. In every patient the concentration of coliform organisms was reduced after the administration of sulfamilylguanidine, but this reduction was not consistent, and much additional study is necessary to determine accurately the effect of this drug on the intestinal flora of human beings. In Case 4 the estimated number of coliform organisms per cubic centimeter of stool fell from 16,720,000 to 10,000 after the drug had been given for 14 days. It is to be borne in mind, however, that this is the most extreme change that we have observed, and, furthermore, this patient received sulfathiazole intravenously and by mouth in addition to the sulfamilylguanidine.

A conscientious effort was made to detect any evidences of toxicity in the patients who received sulfamilylguanidine. Although the drug was given by mouth, none of the patients complained of nausea or vomiting. Case 3, who received 24 Gm of sulfamilamide by mistake, continued to take sulfamilylguanidine without any ill effect. It is also noteworthy that in Case 4 a most extensive rash developed from the use of sulfathiazole. This rash faded promptly after the withdrawal of the compound, despite the fact that sulfamilylguanidine was continued over eight hours. This series of 12 patients is too small to permit one to make any statements about the toxic manifestations that may result from the use of sulfamilylguanidine.

The dosage of sulfamilylguanidine has varied in the patients reported in this paper. We have come, however, to give an oral administration of 50 mg per kilo of body weight every eight hours as the standard dose. We believe that it is necessary to continue this amount of the drug for at least a week before any operative procedure is attempted, and in every case it is necessary to correlate the administration of the drug with the bacterial count before planning a resection of the large bowel.

SUMMARY

This presentation of the records of 12 surgical patients, who received sulfamilylguanidine before operations upon the colon, is to be looked upon merely as the initial step in a far-reaching clinical study. It is not justifiable to formulate any conclusions from such a meager number of observations. One can, however, in all fairness, contrast the postoperative progress of each patient receiving sulfamilylguanidine with the progress that might have been expected had the drug not been given. From this point of view, it seems highly probable that Cases 3 and 5 would have died if the concentration of coliform bacteria had not been reduced before operation. Furthermore, it is almost certain that without the use of sulfamilylguanidine the intestinal wounds in Cases 1, 2 and 4 would have failed to heal *per primam*. Of the remaining seven patients, only two can be regarded as significant in estimating the value of sulfamilylguanidine for large bowel surgery. These are Cases 10 and 12, upon whom open anastomoses were successfully performed without the slightest evidence of subsequent infection.

The convalescence of the patients described in this report justifies the impression that sulfamilylguanidine is a real adjuvant in colonic surgery.

The chief value of this study is the fact that it points to a new field of usefulness for chemotherapeutic agents that possess the properties of sulfanilyl-guanidine

The author wishes to thank Mr Max Broedel for the illustrations which were made from the written records of the operations

REFERENCE

- ¹ Marshall, E K, Jr, Bratton, A C, White, H J, and Litchfield, J T, Jr Sulfanilyl-guanidine A Chemotherapeutic Agent in Intestinal Infections Bull Johns Hopkins Hosp, 67, 163, 1940

DISCUSSION—DR LEO BRADY (Baltimore, Md) Through the courtesy of Doctor Firor, and his associates, I have had the opportunity of using this drug in two patients The first was a female, age 25, in whom an endometriosis had been mistaken for carcinoma of the sigmoid, with involvement of the uterus When I saw her, the uterus and ovaries and six or eight inches of intestine had been removed and a colostomy performed She was only 25 years old, and was not content to continue with the colostomy, she was willing to have anything done to overcome that She was given this drug for eight days At operation, I was unable to effect any type of regular anastomosis so I employed the technic advocated by Balfour 25 years ago, of uniting the ends over a rubber tube and bringing the tube out through the anus I intended to establish an artificial intussusception, as Balfour recommended, but was unable to do more than bring the two open ends into apposition The patient had no vomiting, no nausea and a perfectly uneventful recovery

The second patient had recurring Hunner's ulcers, bilateral hydronephrosis and a contracted bladder I treated her by fulgurating the ulcers, but the bladder was so contracted that each time this was done it was necessary to anesthetize her Finally she developed stones in the left ureter She was given sulfanilyl-guanidine, the stones were removed and the left ureter implanted into the sigmoid She had a slight elevation of temperature for a few days, but no signs of peritonitis I operated upon her two weeks ago She still has bladder incontinence but can control the urine that she passes through the rectum In a few weeks I intend to implant the right ureter into the rectum

Neither of these women had any nausea nor vomiting, and were able to resume taking the drug almost as soon as they came out of the anesthetic

DR HARVEY B STONE (Baltimore, Md) Through the kindness of Doctors Firor and Marshall I have employed this drug in six cases I shall not go into details, but there was involvement of the colon of one kind or another in each case They have all survived operation I think one at least belongs in the category of the "cicus case" you saw in Doctor Firor's picture There was a perforation between the colon and the stomach as a result of long-standing colitis, and, in addition to that, a perforating abscess at the splenic flexure She survived the operation which seemed an impossibility at the start, and she has gone home well How much value to attribute to the drug it is hard to say Several of the cases were the routine cases you expect to get well anyhow They all did well with the drug It will require a lot of additional experimental work to really evaluate it

I want to emphasize a few points to which Doctor Firor called attention The drug possesses the two remarkable and more or less contradictory properties of being more readily soluble in water than any other sulfonamide

compound, and on the other hand is less absorbable from the alimentary tract. Ordinarily, one thinks the property of absorbability as being in proportion to the property of solubility. In this case it is not. In addition to these physical properties it apparently has a more specific attack on the colon group of organisms than any other drug. The combination of these three qualities—the solubility in water, the lessened absorbability from the alimentary tract, and the specificity for the colon group—obviously, make it an agent almost ideally designed for attack upon the bacterial flora of the large bowel. There is one other point in its practical administration I should like to point out. You apparently get the highest degree of effectiveness at the end of six or seven days of administration. It takes about that time of preliminary administration of this drug to insure the fullest bacteriostatic effect in the colon group of organisms and this effect rapidly disappears when the drug is withdrawn, and after several days of cessation of giving the drug, the bacteria reappear rapidly. Therefore it seems wise to give it for six or seven days prior to the planned operation and to continue the administration of the drug six or seven days after operation, until wound healing in the suture line has progressed to the stage where the alteration in the bacterial count is no longer of significance.

I would like to ask Doctor Frior to say more about the dosage. I think we have been giving 4 Gm. of the drug twice a day.

DR ARTHUR M. SHIPLEY (Baltimore, Md.) Several weeks ago Doctor Frior was good enough to put this drug at our disposal at the University Hospital. Dr. Monte Edwards is especially interested in surgery of the rectum and colon, and he reported to me, a few days ago, that he had recently resected the sigmoid for carcinoma and had performed an open end-to-end anastomosis without any subsequent evidence of infection in the wound. He reported also that there had been the same amazing drop in the bacterial count during preparation prior to operation.

DR FRANK H. LAHEY (Boston, Mass.) Have there been noted any contraindications or any evidences of toxicity in the use of this drug?

DR WARREN M. FRIOR (Baltimore, Md., closing) With reference to the degree of absorption, we have found that the blood level concentration ordinarily runs between 2 and 4 mg. per cent, and in only two instances did it go over 5 mg. per cent. The dosage was experimented with in this group of patients, and at present we feel that 50 mg. per kilo of body weight every eight hours for a week before operation and a week after operation is a perfectly safe amount to give. In some experimental work, it has been found that far better results are obtained by giving the drug at eight-hour intervals than more frequently or in a single large dose.

In answer to Doctor Lahey I can only say that we have been on the lookout for evidences of toxicity or contraindications to the use of this drug, and have not found any. I talked to Doctor Marshall just the day before yesterday. He has been using sulfanylguanidine in a series of patients with bacillary dysentery with splendid results, when it is given in the first three days of illness. This report will appear in the January issue of the Bulletin of the Johns Hopkins Hospital.

In summary, we feel that we are just at the beginning of our experimental studies on the use of chemotherapeutic agents in the large bowel.

PNEUMONECTOMY^{*}

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THE PRESENT STATUS of pneumonectomy is somewhat analogous to that of partial gastrectomy during the years immediately following the first gastric resection by Billroth. In the minds of many of the medical profession—physicians and surgeons alike—the operation pneumonectomy connotes a dramatic and ill-advised undertaking accompanied by a terrific surgical attack and fraught with unwarranted hazards. It is the purpose of this communication to refute such ideas and to relate a personal experience with 18 cases of complete pneumonectomy and subtotal resection of the lung. This work has been undertaken chiefly at Bellevue Hospital, and it is here, also, that Courmand^{4, 5} and Maier⁹ have been carrying out their physiologic, and Missall¹⁰ his anatomic, studies. According to autopsy statistics carcinoma of the stomach and intestine are the most frequent forms of cancer, and these are followed by carcinoma of the lung, which has an incidence of about 10 per cent of all malignancies found at necropsy. Like cancer elsewhere, carcinoma of the lung invades, metastasizes, and is fatal unless removed early. Unfortunately, irradiation therapy, whether by radium or roentgen ray, is of little or no avail. Gastric resection for cancer of the stomach is not only accepted but uniformly recommended as the procedure of choice by the medical profession. In St. John's, Whipple's and Raiford's¹⁶ series of 18 cases, 430 (59.8 per cent) were explored, with a 32.1 per cent mortality, and only 9, 1.3 per cent of the total, or 23 per cent of the resections, were alive at the end of five years. In Abrahamson's and Hinton's¹ series of 444 cases, 148 (33.3 per cent) were operable, and in only 16.2 per cent of these, or 5.4 per cent of the total, was gastric resection possible. Of the operated cases 77 (50 per cent) were operative mortalities. Although the various reported series of pneumonectomies for cancer of the lung are, of course, much smaller than the above and cover much shorter periods, still the results compare most favorably.

In 1939, Overholt¹² published a list, collected from the literature, of 58 pneumonectomies for malignant tumors, there were 38 deaths, or a mortality of 65.5 per cent. At the same time he reported his own series of 15 cases with five deaths, a 33.3 per cent mortality. In 1940, he¹¹ published his personal series of 75 cases of carcinoma of the lung, in which the diagnosis had been proved histologically. In 38 (50.6 per cent) of these, exploratory thoracotomy was performed, the mortality is not stated. In this group, 17

^{*} Read before the New York Surgical Society, December 11, 1940. Submitted for publication October 23, 1940.

pneumonectomies were performed with six deaths (35 per cent) Of these pneumonectomies, ten were complete, with individual ligation of the hilar structures, in four, mass ligation of the hilum was performed, and in three, the technic was not stated

In a series of 86 pneumonectomies for cancer reported by Ochsner and DeBakey,¹¹ including seven of their own, there was an operative mortality of 64 per cent, and a recovery of 36 per cent In 31 of these cases, there was individual ligation of the hilar structures, in 17, there was mass ligation at the hilum and in the others, the technic is not clearly stated Reinhoff¹² gives a mortality of 10 per cent in 20 cases

Historical—Pneumonectomy was first suggested by Truc, in 1881, although he never attempted it himself His suggestion, however, may have been based upon the experimental work of Gluck, in 1881, who showed that animals survived the operation Quoting Carter, *et al* : "In 1892, Hassler, after the removal of one lung in a dog ten weeks old, found that the remaining lung, after six months, completely filled the thorax, and showed histologically normal structure with alveoli of normal size"

Mohlgaard and Roosing (1910) recognized that true hyperplasia of the remaining lung following pneumonectomy occurred only in young animals as against a compensatory dilatation in the adult animals

In 1910, Kummel performed the first human pneumonectomy This was for carcinoma, and the patient died on the sixth day Following this, occasional pneumonectomies were performed unsuccessfully for bronchiectasis and suppuration, two of which were reported by Lilienthal, until 1931, when Nissen reported a successful pneumonectomy, by mass ligation, for bronchiectasis Graham and Singer reported the first successful operation for bronchogenic carcinoma in 1933, and were promptly followed, in the same year, by Reinhoff and then by Overholt, with similar successful results Since then the list has grown steadily In April, 1935, Lyle⁶ presented a patient before the New York Surgical Society upon whom he had performed a pneumonectomy for carcinoma Now pneumonectomy is performed without undue risk and with increasing success for pulmonary cancer, suppuration and bronchiectasis, and, occasionally, for tuberculosis

Terminology—Even to-day, the term *pneumonectomy* is so loosely used that it may signify either of two quite distinct operative procedures first, it may mean the removal of the lung by the technic of mass ligation of the hilum of the lung *within the pleura* This may result in amputation of the lung across the hilum just within the pleura, or, as is much more frequent, a tourniquet is placed about the hilum and a varying fringe of lung tissue remains after the pneumonectomy—partial or subtotal There is still another type of procedure whereby, for example, the right middle and lower lobes are first removed and then, at a later date, a lobectomy of the right upper lobe is also performed True, all of these methods describe some form of pneumonectomy, but I believe the proper terminology for any such procedure should be *pneumonectomy intrapleural* or *pneumonectomy sub-*

total These are absolutely different procedures from a complete pneumonectomy performed *within the mediastinum* by opening the mediastinal pleura, with individual ligation of the hilar structures, and with removal of such lymph nodes as may be possible. In my opinion, the terms *pneumonectomy* or *complete pneumonectomy* should be reserved for this type of operation. This is important because in going over the reports of pneumonectomies one encounters a confusion of technics and terms. Pneumonectomy for cancer should always be complete, with individual ligation of the artery and veins, bronchial closure, and removal of as many of the bronchial nodes as possible. If the hilum of the lung is not sufficiently free to permit this, the case is inoperable, as the growth has already extended beyond the reach of surgery. In tuberculosis also, when pneumonectomy is contemplated, it should be complete. With bronchiectasis and pulmonary suppuration, however, intrapleural subtotal pneumonectomy may be, and in fact usually is, the procedure of choice and may be accomplished in one or several stages.

Anatomy—Comparatively little attention has been given to variations and anomalies of the vessels at the hila of the lungs. It is stated in the ordinary anatomic descriptions that the pulmonary artery may sometimes divide within the pericardium, that occasionally there may be three pulmonary veins on the right or a single one on the left, and the bronchial arteries vary from one to three on each side. In one instance, we have encountered three veins on the right. Recently, Harris and Lewis⁶ cited the case of a patient in whom an anomalous branch from the aorta, about the size of the celiac axis, entered the left lower lobe through the broad ligament. Some years ago, we encountered an identical anomaly during the performance of a right lower lobe lobectomy. We have been interested in the variation in size and length of the pulmonary artery and veins, and in the shape of the latter. Occasionally a vein appears as a conical prolongation of the auricle and, furthermore, the pericardium may be extremely thin about the veins. Miscall has made a number of dissections in the fresh cadaver with this in mind, and has demonstrated to us considerable differences in the lengths and arrangements of the vessels and their first branches and the prolongation of the pericardium on the veins. In all surgery about the hilum of the lung such variations should be kept in mind and anomalous vessels sought for.

Physiology and Mechanics—There are two interlocking questions, the answers to which are of vital concern to these postpneumonectomized patients: (1) What happens to the pleural cavity after removal of the lung?, and (2) what happens to the remaining lung? If there is no infection the pleural cavity is normally obliterated, as Rienhoff¹⁷ says, by a prompt rise of the diaphragm, slight curvature of the spine, with a falling downward and inward of the ribs, some shift of the mediastinum to that side, with compensatory emphysema of the opposite lung, marked thickening of the parietal pleura, and the gradual organization of the plasma, which fills the space after operation so that a loose mesh of organized fibrin and fibrous tissue results. In this meshwork small collections of fluid may persist. It has

been our practice to aspirate the pleural cavity postoperatively, as often as necessary to relieve symptoms and to keep the intrapleural pressure within or near normal limits. Rienhoff also thinks that the compensatory emphysema of the opposite lung is partly hypertrophy and partly simple dilatation of the air sacs without rupture or destruction of the elastic tissue as occurs in true emphysema.

Studies in embryology and comparative anatomy show that actual growth of the lung continues after birth, probably until about the seventeenth year. Carter and Longacre,³ and later Longacre,⁷ have been working on this problem from the physiologic aspect with pneumonectomized puppies and adult dogs for seven years. At the end of three years, their results seemed to show that following pneumonectomy the adult dogs developed emphysema sufficient to impair their activities, whereas after nine months the puppies compensated as well as their controls when subjected to similar stress. At the end of seven years, however, Longacre feels that eventually the puppies developed evidence of emphysema in comparison with their controls. On the clinical side, Graham and Overholt both have patients carrying on their usual occupations over five years after pneumonectomy, one had a thoracoplasty and the other did not. It will only be by a careful follow-up of such patients that we shall learn whether or not to advise a thoracoplasty to prevent overdistention of the opposite lung and symptoms of emphysema or fibrothorax.

For several years, under the direction of Richards, Courmand,^{4, 5} and Maier, we have been carrying on studies along similar lines with tuberculous patients both before and after surgery. Recently, we have included also our pneumonectomy group. These procedures include

(1) *Lung Volume Measurements* These are divided into vital capacity and residual air, the sum of which form the total capacity. Normally, the vital capacity forms about 75 per cent of the total capacity, and the residual air 25 per cent, varying somewhat with sex and age. "Increase in the proportion of residual air and decrease in the proportion of vital capacity may indicate pulmonary fibrosis, congestion of the lung, emphysema (compensatory or pathologic) or presence of a poorly ventilated air pocket in the lung."

(2) *Breathing Capacity* This is less well-understood, and "is the measure of maximum ventilation per minute or maximum breathing capacity. In other words, it tests the efficiency of the chest bellows for air displacement."

(3) *Ventilation under Varying Physical Activity* This is estimated "(a) under basal conditions, (b) during a one-minute period of exercise, and (c) during the period of recovery following it."

(4) *Breathing Reserve* "The breathing reserve is the excess breathing capacity, beyond the actual ventilation used."

(5) *Efficiency of Ventilation* "From each liter of air circulating in the lung a variable amount of oxygen is removed by circulating pulmonary blood, during rest, exercise and recovery. In pathologic states, poor coordination between aeration and blood perfusion of the lungs, or parts of the lungs, may result in inefficient ventilation."

(6) *Study of Respiratory Gases in Arterial Blood* "In normal subjects at rest and during early recovery of the standard exercise, the arterial blood leaving the lung is between 94 and 98 per cent of the maximum oxygen saturation. Values below this range usually mean that a certain proportion of the blood has circulated through the improperly ventilated alveoli." These estimations, also made in the immediate postoperative period, are of considerable prognostic aid and are of great help in the application of oxygen therapy.

(7) *Study of the Circulation* "To test the capacity of the heart and pulmonary vascular bed to accommodate an increased blood flow, to test, that is, for any latent pulmonary congestion we have used the venous pressure-infusion test. In this, the level of venous pressure and the vital capacity are followed during the course of a rapid intravenous infusion. If the vital capacity decreases significantly during this infusion it is evidence of congestion in the pulmonary vascular bed, due either to a local state of the capillaries or to an obstacle to the flow of blood in the pulmonary veins, or to latent left heart failure. If the venous pressure shows an abnormal increase there is suggestive evidence of embarrassment of the right side of the heart under the conditions of the test."

Preoperatively, we think that, together with the other clinical and usual laboratory observations, such studies help us estimate the risk of surgery to the patient and, at six-month intervals postoperatively, we feel that we are enabled to gain a better insight into the respiratory and cardiorespiratory status of these pneumonectomized patients. Our work has hardly begun, and we realize that it will take several years to evaluate our results.

A brief resume of and comments upon the 18 cases may be of interest.

ABBREVIATED CASE REPORTS

(A) PNEUMONECTOMY FOR CANCER

Ten Cases

Case 1—J M, male, age 52, had noticed a cough, with yellowish sputum for a year. Seven and five months previously he had had severe hemoptyses. During the three months prior to admission he had lost 25 pounds in weight, and had become weak. Roentgenograms showed a large, solid mass in the right lower chest. Bronchoscopy was not undertaken. Operation revealed a large tumor occupying most of the right lower lobe. The lung was free and the hilum normal. A complete pneumonectomy was performed. As the bronchus was ligated the patient suddenly died. *Histologic Diagnosis* Bronchogenic carcinoma. *Comment* Peribronchial novocain injection might have prevented this fatality.

Case 2—T M, male, age 45, had noticed sharp pain under his right scapula and in right upper arm for about three months, and there had been a loss of 25 pounds in weight. Roentgenograms showed a solid, spherical mass in the left midchest, well away from the hilum. Bronchoscopy was not undertaken. Operation disclosed a completely free and normal hilum. This was dissected, the vessels and bronchi ligated, and the bronchial stump sutured. In the lower lobe there was a firm mass adherent to the posterior chest wall. The remainder of the lung was not adherent. On removing the lung, it was found that the mass in the lower lobe was invading the pleura and ribs. *Histologic Diagnosis* Bronchogenic carcinoma.

The patient made a smooth postoperative recovery, and was completely relieved of his pain. The wound healed cleanly. He did not gain weight, and six weeks after

operation developed a transverse myelitis. He died on the forty-seventh day from spread of his tumor.

Case 3—T. G., male, age 43, had complained of blood-streaked sputum for two months before admission. Bronchoscopy with biopsy revealed a bronchogenic carcinoma in the right middle lobe bronchus. Roentgenograms of the bones were negative. Operation revealed a small tumor at the mouth of the middle lobe bronchus. The mediastinal nodes were enlarged and firm. Complete pneumonectomy was performed, together with a dissection of the mediastinal nodes. The patient made an uneventful convalescence, and the wound healed cleanly. One month later a metastasis was noted in the second right rib. This was removed, and radon seeds implanted. The patient went home but returned to the hospital very shortly, and pursued a downhill course, with intense pain in his right shoulder. A cordotomy was performed which gave relief during the remainder of the patient's life, which was only three weeks. The patient died seven months after his pneumonectomy.

Autopsy showed recurrence of the tumor in the right pleural cavity and ribs on the right side, with involvement of the sympathetic chain on the right and several thoracic vertebrae.

Case 4—R. B., male, age 60, had noted a "wheeze" in his left chest for three years, and a slight cough, with mucopurulent sputum, occasionally blood-streaked, for one year. Nine months before admission he developed pleurisy in the left chest from which 200 cc of straw-colored fluid was removed. Two months before admission he was bronchoscoped and a tumor noted in the left main bronchus. On admission to the hospital, he was rebronchoscoped, with similar findings. The biopsy was reported as a bronchogenic carcinoma, transitional cell. Complete pneumonectomy was performed. The lower lobe showed extensive suppuration and bronchiectasis beyond the tumor. The patient had a very stormy convalescence, due to auricular fibrillation and the development of pneumonia in his right lung, from which he finally recovered only to develop an empyema in his left pleural cavity. This was drained, with a rib resection. At one time there was a small bronchial leak which persisted only a few days. At the time of operation a group of large aortic nodes were removed. No evidence of tumor was found in any of the nodes but on removing them the recurrent laryngeal was injured. He was finally discharged from the hospital, eight months postoperative, without any sign of recurrence. The reason for his prolonged hospital stay was that he had no place to go. After seven months' drainage the empyema sinus closed.

Case 5—W. R., male, age 55, had a history of symptoms for ten months, starting with gripe and a persistent cough, with about 90 cc sputum a day. There had been a loss of 30 pounds in weight. He had been attending the Bellevue Hospital Medical Clinic for four months. He was then admitted to the hospital and observed for 17 days before bronchoscopy was undertaken, which revealed a tumor in the right main bronchus just below the middle lobe opening. Biopsy showed carcinoma, transitional cell. Operation was delayed because of an upper respiratory infection. Sputum cultures showed *Streptococcus haemolyticus* and *Streptococcus viridans*. A complete pneumonectomy was performed five weeks after admission. There were enlarged mediastinal lymph nodes. The patient developed an extensive pneumonia, and died 48 hours postoperative. In the operative specimen, the bronchial nodes on section showed extensive tumor infiltration but there was none found in the deeper nodes. *Comment*: Operation should have been delayed and the patient should have received sulfapyridine immediately before and after operation.

Case 6—E. B., male, age 31, developed a cough one year before admission and, during the interval, there had been several episodes of hemoptysis. Roentgenograms, seven months before admission, were reported negative. Others, taken one month before admission, showed a density throughout the left lung, with retraction of the mediastinum to the left. He had coughed about 90 cc of sputum a day throughout his illness, and there had been some dyspnea on exertion throughout the year. There was no weight

loss After admission, bronchoscopy showed a mass in the left main bronchus. Biopsy report was bronchogenic carcinoma, transitional type. A complete pneumonectomy was performed three weeks after admission. No enlarged mediastinal nodes were noted, but as the hilum was dissected it was found that a tongue of tumor extended up along the posterior wall of the trachea beyond the carina. Inasmuch as this had not been noted on preliminary palpation and the vessels had all been ligated, pneumonectomy was completed. The bronchus was ligated and sutured at the level of the trachea, but a small piece of tumor on the posterior wall of the trachea was left *in situ*. The patient made an uneventful convalescence, and the wound healed cleanly. He was discharged one month postoperative. He has gained weight since, and when last seen, four months postoperative, was still well. He was complaining of a dry cough at that time, and bronchoscopy showed the end of the bronchial ligature protruding into the bronchus. Inasmuch as this was well embedded in the tissue it could not be pulled out. No mediastinal enlargement was seen roentgenologically at that time. The patient had resumed work.

Case 7—W J, male, age 54, gave a six months' story of loss of weight, vague substernal pain, and recent hoarseness and sore throat. Roentgenograms showed a shadow in the right middle lobe. He was bronchoscoped twice. The first was reported as negative, and the second showed the presence of a tumor in the right middle lobe bronchus, biopsy from which was reported as bronchogenic carcinoma, squamous cell. A complete pneumonectomy was performed. The lung was entirely free, there was no involvement of the mediastinal nodes, and the tumor was found, as described, in the right middle lobe bronchus. The patient made an uneventful convalescence, and the wound healed cleanly. Convalescence was complicated by an infection in one eye and also by a cystitis, both of which cleared up. He was discharged to the convalescent wards on the fifty-second day, and has since shown no sign of recurrence.

Case 8—M A, male, age 37, had noticed pain in his right shoulder and upper arm for six months. There had been a dry cough for two months. No loss of weight. Roentgenograms revealed a large, homogenous and well-circumscribed shadow in the upper part of the right upper lobe. Bronchoscopy was not undertaken. Operation revealed a large, solitary yellowish tumor in the right upper lobe, adherent on the mediastinal side and at the apex. A complete pneumonectomy was performed. As the lung was removed, it was evident that particles of tumor were left along the innominate vein and subclavian vessels on the right. The patient did very well for 12 days when his bronchial stump broke open, following which he developed an empyema. He went rapidly downhill, and suffered intense pain in the right shoulder and arm which could not be relieved. Cobra venom, alcohol injections and morphine were all ineffective. He died on the forty-second postoperative day.

Autopsy showed an extensive recurrence of the tumor in the right pleural cavity, involving the vertebrae, mediastinum, parietal pleura, and bronchial stump. No tumor elsewhere in the body. The tumor was reported in the operative specimen as a hypernephroma. Kidneys and adrenals, however, were normal at autopsy. It is possible, therefore, that this may have been an anaplastic type of bronchogenic carcinoma.

Case 9—I S, female, age 33, had no relevant previous history. A dense shadow in the left upper lobe was discovered in taking routine roentgenograms while searching for a focus of infection to account for a choroiditis. Bronchoscopy was not undertaken. Physical examination was negative for nodes, but showed marked dullness over the left apex. Aspiration biopsy was reported as showing a chronic inflammatory process. A complete pneumonectomy was performed. There were extensive adhesions to the anterior chest wall and along the mediastinum. It was at first thought that these were not due to invasion of the tumor, therefore, the operation was completed, inasmuch as the hilum was entirely free. In removing the lung, however, it was found that the tumor had invaded the anterior chest wall and that there was a group of enlarged subcaracoid nodes.

Therefore, along with the lung, the intercostal bundles and muscles of the first, second, and third spaces, together with the second and third ribs, were removed from the sternum to the midaxillary line, together with the group of nodes beneath the coracoid. The patient made a rather slow convalescence, and her wound healed cleanly. Before discharge she was given 2,300 r units of roentgenotherapy. The tumor was reported histologically, as a reticulum cell sarcoma. The patient left the hospital on the forty-second day.

On July 1, 1940, about two months postoperative, there was no evidence of recurrence either by palpation or roentgenologically, but the patient still had pain in the back of her chest, probably due to retraction and high negative pressure. This was in part relieved by injection of alcohol into the fourth, fifth, sixth, and seventh intercostal nerves. Five months postoperative, the mediastinum appeared normal, and she had gained weight, but a small, firm node had appeared above the left clavicle.

Case 10—V W, male, age 63, had an hemoptysis ten months before admission, followed by a month of daily cough with blood-streaked sputum, during which time he lost between five and ten pounds of weight. Three months prior to admission, he began to have inconstant blood-streaked sputum, since which time he had lost between ten and 15 pounds. On admission to the hospital, he was found to have a lesion involving the upper part of the left upper lobe. This could not be seen by the bronchoscope. At operation, a tumor was found which was operable. A complete pneumonectomy was performed. Convalescence was uneventful except for undue pain and a rather bizarre white count running between 4,000 and 16,000, with 10 to 25 per cent polynuclears.

In reviewing these ten cases, first, the anterior approach was employed in all, and, second, there were two operative deaths—one during operation and one two days later of pneumonia. The first mortality might have been prevented by injecting novocain about the main bronchus, which we have done since. The second, in view of his recent respiratory infection and sputum cultures, should have had his operation postponed, and have had sulfapyridine administered just prior to and following surgery. Three died of their tumors in from 42 to 210 days after operation. The bronchial stump leaked temporarily in one instance, and broke open in a second, due to tumor invasion.

In one case, fluid had been present in the chest. This, however, was due to pneumonia and not to the tumor *per se*. I do not feel, therefore, that the presence of fluid necessarily precludes surgery, unless tumor cells can be demonstrated, the fluid is bloody, or there are other frank signs of pleural metastases.

Of these ten cases, only two patients (Cases 7 and 10) can be considered as ideal. Of the five who now survive, one had extensive suppuration and bronchiectasis at the time of pneumonectomy, one had an inremovable extension of cancer along the posterior wall of his trachea, and one had extensive invasion of her chest wall and lymph node metastases. Yet all of these patients were greatly benefited by operation—one was working four months later, another was living comfortably in a permanent home, and the third is with her family, leading a somewhat restricted life, and will undoubtedly require further radiation therapy. The two theoretically ideal cases were of men in their sixth and seventh decades, and appeared to be somewhat older than their stated ages. Neither has a home, and because of their general arterial status their future is problematic. One is in a convalescent home and the other about to go to one.

In passing, it might be of interest to mention the exploratory thoracotomies for cancer in which pneumonectomy was found to be impossible. During this same 17-months' period 14 such procedures were performed by the staff. There were two deaths from empyema, in both instances specimens for biopsies from the lung had been taken. All of the other patients made prompt recoveries with very little reaction from their operations. One patient even returned to his work as a carpenter, although his pleura was covered with metastatic nodules and the hilum "frozen." One additional patient, age 60, was explored because a bronchoscopic biopsy had been reported to be carcinoma. At operation, a large, firm mass involving the hilum was found. In attempting to free this the superior vena cava was torn with fatal results. Autopsy disclosed the mass to be a tuberculoma. Needless to say, if the biopsy diagnosis had been correct, surgery would not have been attempted, and, furthermore, the case should have been recognized as inoperable. Finally, there were 18 patients with a proven diagnosis, by biopsy, of bronchogenic carcinoma, who were considered unfit even for exploration—all of these died while in the hospital.

Thus, of the total 42 patients with cancer of the lung, all except six from a municipal hospital, 66.6 per cent seemed to warrant exploration, and in ten instances, 33.3 per cent complete pneumonectomy was feasible. We should be able to look forward with considerable assurance to a definite betterment of these statistics.

(B) BRONCHIECTASIS AND SUPPURATION

Six Cases

Case 11—G W, male, age 23, with extensive bronchiectasis and suppuration throughout left upper and lower lobes, productive of 840 cc of foul sputum a day, even after bronchoscopic treatment and pneumothorax. A complete pneumonectomy, with individual ligation and suture of hilar structures, was performed. *Result* Death from pneumonia and empyema, 72 hours postoperative.

Case 12—J H, male, age 26, with extensive suppuration of his entire right lung. He had been under bronchoscopic treatment for three months. A complete pneumonectomy, with individual ligation of the hilar structures, was performed. *Result* Death on the twelfth day of sepsis, empyema, and eventual leakage of the bronchial stump.

Case 13—M K, male, age 36, with extensive cystic bronchiectasis of entire right lung. A subtotal intrapleural pneumonectomy was performed. *Result* The patient developed an empyema, the remaining stump of lung dilated, and the mediastinum shifted sufficiently to fill the chest, which had shrunken markedly in size. One year later, the patient has a small amount of morning sputum, but is otherwise well.

Case 14—S K, male, age 28, with chronic suppuration in left lower lobe following a lung abscess. A lobectomy was performed. Following this, his suppuration extended to the upper lobe, and, eventually, this lobe was removed. He is now awaiting thoracoplasty to close his empyema.

Case 15—K G, male, age 37, who had suffered from diffuse bronchiectasis in his right lung since a crushing injury of the chest five years previously. Bronchoscopy showed a stricture of the main bronchus. Operation revealed a healed fracture of the right main bronchus, with resulting stricture. A subtotal intrapleural pneumonectomy was performed. The patient made a smooth convalescence, without infection of any sort. He is awaiting further studies to determine the advisability of thoracoplasty.

Case 16—S G, female, age 27, had suffered from dry bronchiectasis of the left lower lobe for years with frequent attacks of pneumonia. Roentgenograms showed what was considered to be a large cyst of the left upper lobe. Operation revealed a large thin-walled cyst occupying the entire upper lobe. This communicated through a very minute opening with the lower lobe, which was completely fibrosed about a group of very large thick, dilated bronchi containing only a small amount of secretion. Except for the communication with the lower lobe there was no demonstrable bronchus to the upper lobe. Subtotal intrapleural pneumonectomy was performed. The patient recovered without infection. She is now awaiting a decision as to thoracoplasty, because of a small bronchial leak that developed two months after operation.

As it so happened, in this small group all the subtotal intrapleural pneumonectomy patients recovered and the two with complete pneumonectomy succumbed to the operation. It is fair to say, however, that these two had highly infected and grossly suppurating lungs at the time of operation and hence were most precarious operative risks.

(c) TUBERCULOSIS

Two Cases

Case 17—N N, male, age 34, had had an extensive two-stage extrapleural thoracoplasty of eight ribs, and an apicolysis, on the right. His apical cavity still remained open. After several months of sanatorium care, a complete pneumonectomy with individual ligation of the hilar structures was performed, after bronchoscopic examination showed the main bronchus to be normal. Following operation the patient exhibited extreme dyspnea, and died on the third day. During this period his arterial oxygen did not drop below 85 per cent but in spite of this and an oxygen atmosphere of 60-70 per cent his dyspnea persisted.

Autopsy failed to show a cause of death. The pleura was clean, the bronchial stump tight, and the other lung free of disease. This suggests true mediastinal flutter, which might have been controlled by tight packing, inasmuch as firm closure of the chest wall was impossible due to the former thoracoplasty.

Case 18—M S, female, age 32, who had been operated upon many times because of a mixed infection empyema and bronchial fistula. Inasmuch as her fistula and positive sputum persisted she requested pneumonectomy. The bronchus was the site of a healed tuberculous stricture, and there was moderate contralateral infiltration. Complete pneumonectomy with individual hilar ligation was performed, and the chest firmly packed. She did rather well at first but then developed increasing dyspnea and signs of bronchopneumonia in the opposite lung and died on the ninth postoperative day. Roentgenograms showed what we thought to be an exacerbation of her tuberculosis.

Notwithstanding these two fatalities I feel that pneumonectomy is indicated in certain selected cases of pulmonary tuberculosis, more especially those with a healed stenosed bronchus. This should always be complete with individual ligation of the hilar structures. Probably the mortality will always be higher in this group.

Summary—A history of the development of the operation pneumonectomy has been given briefly and its application to certain types of disease described.

The anatomic, mechanical, and physiologic factors that should be considered have been discussed.

Eighteen clinical cases have been summarized, in which pneumonectomy has been performed during the period between May 1, 1939, and October 1,

1940 In ten of these, the operation was performed for cancer, with two operative deaths. Complete pneumonectomy was performed in each instance.

In six, the operation was performed for bronchiectasis, suppuration, or cystic disease. There were two operative deaths. In both of these a complete pneumonectomy was performed, in the other four, a subtotal intrapleural pneumonectomy was the procedure.

The third group comprises two cases of advanced chronic pulmonary tuberculosis. Both died.

A comparison is given of the results of surgery for cancer of the stomach and of the lungs. The operative mortality is less for exploratory thoracotomy and pneumonectomy than it is for exploratory celiotomy and gastric resection for cancer.

CONCLUSIONS

(1) The term "pneumonectomy" as used at present is inexact. There should be more specificity, hence "complete pneumonectomy" and "subtotal" or "incomplete intrapleural pneumonectomy" are suggested. As to complete pneumonectomy, I am in full accord with Rienhoff when he says "No lung or peribronchial tissue or lymph nodes should be left behind. If such is the case a complete pneumonectomy has not been performed." This always means individual ligation of the vessels and closure of the bronchus within the mediastinum.

(2) In cancer, when a pneumonectomy is considered, it should always be *complete*. Intrapleural mass ligation of the hilum is to be condemned. Again to quote Rienhoff "Only those patients in whom the lung is, in the main, free from the chest wall, and the hilus uninvolved, should be subjected to operation, otherwise a relatively safe surgical procedure will be brought into disrepute."

(3) Pneumonectomy is the procedure of choice in certain cases of bronchiectasis, cystic disease, or suppuration. It may be either complete or subtotal intrapleural. Probably the latter will be safer in the majority of instances because of the possibility of infection.

(4) When pneumonectomy is indicated for pulmonary tuberculosis, it should always be complete. This will lessen the danger of dissemination of the disease and persistent bronchial fistulae.

(5) Operative mortality statistics for pneumonectomy should be clearly differentiated. First, according to the disease—cancer, bronchiectasis and suppuration, or tuberculosis, and, second, as to whether or not the pneumonectomy was complete or a subtotal intrapleural procedure.

(6) There is but little in the literature about vascular anomalies of the hila of the lungs. These should be recorded when encountered.

(7) It is important to study the respiratory and cardiorespiratory physiology of patients after pneumonectomy, in order that we may advise, and treat more intelligently, this growing group of patients. These studies should be threefold: (1) as an aid to ascertain the operative risk of the patient, (2) to

study the patient subsequent to pneumonectomy, (3) to determine, eventually, whether or not a thoracoplasty should be recommended following pneumonectomy

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DISCUSSION—DR HOWARD LILIENTHAL (New York) The paper by Doctor Berry is an important one from many points of view The exact definition should be noted The significance is total removal of the lung with its section within the mediastinum and with no pulmonary tissue remaining But Doctor Berry admits that, in cases neither cancerous nor tuberculous, the operation may be performed intrapleurally It should then be specifically designated

Discussion of all the divisions of the paper would be impossible at this time For example, the study of measurements of volume, respiratory capacity, ventilation, study of arterial blood and of the circulation in general, might well form the subject of an entire volume Although I am incapable of doing more than to bring the subject to your attention, it is well that Doctor Berry has shown the importance of studying these branches of pathology and physiology in most of the cases which come to the attention of the surgeon, both before and after operation And, naturally, one should be, so far as possible, acquainted with abnormal anatomic facts, particularly, the vascular—arterial and venous—irregularities

In the technic of the operation itself—pneumonectomy—it is the surgeon's art which may well determine the result, as distinguished from his knowledge of the scientific aspect which he must learn from those who work with him

Practically all of this has been discussed in the paper itself, and I mention it now so that the operation itself may not occupy the "center of the stage"

The sudden death of a patient during an intended pneumonectomy has been mentioned. I believe that this misfortune is more frequently observed during intrathoracic procedures than in other operations. I have had this accident happen in two of my cases—in both during ligation of a bronchus. In a third, not one of intended pneumonectomy, I had used an exploring needle to locate, if possible, a metallic foreign body. The "dead" patient came to life after long-continued artificial respiration. He still has the foreign body in or near the mediastinum and I have refused to make further efforts to relieve him surgically of the cough, which he thinks persists because of the presence of the offending little bit of metal.

Whether the employment of a local anesthetic would prevent this accident, it would be impossible to *prove*, even though there were a large number of cases. And, too, there is always the possibility of idiosyncrasy.

The patient in Doctor Berry's series, who coughs because of the presence of a rather long thread of silk within the bronchus, might, perhaps, be relieved by electrocautery through the bronchoscope.

As to intrapleural pneumonectomy in suppurative disease, it seems to me well worth contemplating, because, especially here, complete removal of the diseased parts is not so imperative as it is in cancer or tuberculosis.

DR HERBERT C MAIER (New York) said that he and Doctor Cournand had been investigating various physiologic disturbances and readjustments following pneumonectomy. The patients have been studied before operation and at varying intervals after pneumonectomy. In the immediate postoperative period, one of the problems has been the arterial oxygen saturation, which indicates whether the blood is well oxygenated during its passage through the pulmonary circuit. In those cases in which the patient had a very satisfactory clinical course, it was found that the oxygen content of the arterial blood returned to a normal level within a few days following pneumonectomy. In cases with emphysema or with some complication in the postoperative period, the readjustment is somewhat slower and may take several weeks. These studies of the determination of arterial oxygen have been used as a guide as to how long oxygen therapy should be continued. To rely upon clinical criteria, such as dyspnea and cyanosis, is not satisfactory, these signs are too inaccurate to be a reliable guide as to whether oxygen deficiency is present.

Obtaining blood for arterial oxygen saturation determination is a relatively simple procedure. Blood is usually obtained from the brachial artery and the procedure, once mastered, is no more difficult than the obtaining of blood from a vein.

As for changes in pulmonary function some months following pneumonectomy, final conclusions are not available at present. In those cases in which the tumor was located in a main bronchus, and the lung had undergone considerable atelectasis before operation, the respiratory function is changed very little by the pneumonectomy. An important factor is the relatively slight thoracic deformity which follows uncomplicated pneumonectomy.

A point of great interest, is whether there is actual destruction of the elastic tissue and the early development of emphysema in cases of pneumonectomy in which the organization of fluid results in a marked retraction of the mediastinum and an associated increased size of the remaining lung. We are studying these patients at intervals of several months after operation. The time interval is at present too short for us to draw any final conclusions, but it is Doctor Maier's hope that by continuing the observations it will be possible to arrive at a possible answer to the question whether, in some cases, thoracoplasty should follow the pneumonectomy, in order to diminish the extent of mediastinal deviation and to lessen the effect that the displacement may have on the contralateral lung.

DR CARL EGGERS (New York) brought out the fact that several cases shown by Doctor Berry in his paper, indicated that decided progress had been made in thoracic surgery during the last few years. This presentation should be stimulating to all of us. The technical problems of the radical operation of pneumonectomy have been largely mastered. It is a very difficult operation, one should not lose sight of that. Doctor Neuhof touched upon the possibility of treating some patients by a procedure less exten-

sive than a total pneumonectomy. It is only a small group of cases in which that will be possible. Personally, I have had only one patient with an intralobar carcinoma in whom an upper lobectomy was sufficient. These cases are very apt to have a pleural invasion, and become inoperable from that standpoint.

The greatest technical advance in performing pneumonectomy has been made since Rienhoff stressed the importance of treating the structures of the hilum by individual ligation through an anterior incision. Aside from the importance of the proper technic, however, there are those physiologic problems to consider that Doctor Berry touched upon, and which his coworkers have emphasized. They are not clarified as yet, and progress is still, undoubtedly, going to be made. Then there is another phase which we must not lose sight of, i.e. that in these carcinoma patients we are dealing with cancer which, in the lung, presents the same characteristics as in other organs. We must emphasize the importance of getting the patients early. Just as in carcinoma of the breast or stomach if the patients are operated upon and the lung resected before the lymph nodes are involved, a fair percentage of recoveries may be looked for. It is surprising how long it takes before the diagnosis is made in most of these cases. Both clinicians and roentgenologists must learn to interpret symptoms and findings accurately and earlier, then we may hopefully look into the future for better results.

DR CHARLES W. LISTER (New York) said that with regard to pneumonectomy in children, that some of the most brilliant results are going to be found in this class of case, because the work of Longacre and Carter, in Cincinnati, suggests that there may be an actual increase in the size of the lung after pneumonectomy. Doctor Cournand has been studying the pneumonectomies that we have performed on the Children's Surgical Service at Bellevue Hospital during the past three years. The first was performed by Doctor Bohrer, in October, 1937, so we have studies upon patients with pneumonectomies of more than three years' standing, although others are more recent. These studies all show that the children are able to compensate very well for the loss of the lung. Of course, the pneumonectomies were all undertaken for suppurative disease, and the lung was removed intrapleurally. Therefore, they have not had the complete pneumonectomy that is undertaken for carcinoma. However, all the functioning lung has been removed. When these studies have been completed, and the children have been followed for a greater length of time, I believe that we will find there is an actual regeneration of lung, that the remaining lung can take on the function of the lung that was removed, and that these children will be able to grow up without any impairment in their respiratory function.

DR FRANK B. BERRY (New York) said, in conclusion, that he was particularly grateful for Doctor Lilienthal's discussion. Although the speaker did not mention the various operations—lobectomy *versus* pneumonectomy for carcinoma—he was in agreement with Doctor Neuhof that some cases do well following lobectomy, he is not completely persuaded that every case of carcinoma should have a pneumonectomy performed, though he may be so convinced at some future time.

Doctor Berry thoroughly agreed with Doctor Eggers that a great deal can be accomplished if patients are seen early. Of the cases shown, at this time, one had had symptoms of the lesion ten months, and the other six months, both happened to be favorable cases. Another patient, whom Doctor Berry thought would be favorable, had had symptoms for more than two years. He developed a very peculiar metastasis recently—apparently a solitary metastasis in his pectoralis major muscle on the operated side, although the tumor was deep in his bronchus, and there was no spilling as the lung was removed. That developed about one year after operation.

As to the patient with the silk ligature he had a small piece of tumor in the posterior wall of his trachea. He was well until one month ago when he noticed pain in his chest, and is now back in the hospital with empyema, which developed in one of the small pockets of fluid, which is a source of danger in leaving a chest full of organized fibrin and fluid. Some of the pockets, although sterile at the time, are potential foci for later infection. Doctor Berry did not think, however, that this was the whole story with this patient. The patient is beginning to be hoarse and has a wide mediastinum, probably from recurrence of his carcinoma.

MORTALITY FACTORS IN THE SURGICAL TREATMENT OF ULCERATIVE COLITIS

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THREE YEARS AGO, before this Association, one of us (H. W. C.) discussed the surgical treatment of chronic intractable ulcerative colitis, and presented the case histories of six colectomized patients. Radical procedures were advocated as curative measures where irreversible changes had occurred. The series is now considerably larger. We have performed 90 operations upon 50 individuals. There were 11 deaths, a gross mortality of 22 per cent. The 50 cases subjected to surgery were selected from 301 patients seen and studied on the Gray Service of the Roosevelt Hospital during the past five years (Table I).

The wider experience makes it justifiable to enumerate and discuss factors influencing the operative mortality, and to suggest measures which we believe will help in its reduction. The inflammation and ulceration extending deep into the colonic wall, with the secondary pathologic changes in other tissues that characterize this disease, predispose to a high mortality.

It has been difficult to determine, with any degree of accuracy, the incidence of the disease, and difficult to estimate the exact mortality, for no large series has been reported. We have learned from the Bureau of Records, that in New York City, with a population of 7,347,000 individuals, 1,823 died of cancer of the stomach in 1939. In the same year 1,454 died of cancer of the colon, 804 died of cancer of the rectum, while only 59 died of ulcerative colitis.

A comprehensive understanding of the progress of the disease is essential before mortality rates will be lowered. It is a cyclic recurring disease usually divided into four stages: (1) Phase of acute activity; (2) Phase of convalescence; (3) Phase of quiescence; (4) Phase of early recurrence.

The principal indirect mortality factor in the treatment of ulcerative colitis is that surgery comes too late. The thought of permanent ileostomy, with the dread of caring for an almost continuously discharging stoma on the anterior abdominal wall, militates against early surgery, yet, it has to be tolerated, in order that these unfortunate individuals may live.

The physician who sees these patients early must be impressed with the disastrous effects of delay, particularly when the process has reached an irreversible stage. When he has been enlisted to the cause of earlier intervention there will be real hope of diminishing the mortality.

The two major, direct mortality factors are hemorrhage and peritonitis.

Massive hemorrhage in the acute fulminating stage of the disease has been fatal frequently in the past, even before ileostomy could be contemplated as a preliminary procedure. Our experience with ileostomy performed early after massive hemorrhage has proved, for the most part, unsuccessful. We have decided, for this reason, that profuse hemorrhage is no longer an indication for surgery, and recommend risking the outcome with intelligently administered dosages of vitamin K, if the prothrombin is low, and vitamin C, and transfusions. The spasm which predisposes to hemorrhage is relaxed

TABLE I

TOTAL SURGICAL PROCEDURES

TYPE OF PROCEDURE	NUMBER
ILEOSTOMY	34
PARTIAL COLECTOMY	8
SUBTOTAL COLECTOMY	24
ABDOMINO-PERINEAL RESECTION (removal of entire colon and rectum 4)	7
CAECOSTOMY	1
ILEO-SIGMOIDOSTOMY	6
ILEO-TRANSVERSE COLOSTOMY	2
EXPLORATORY CELIOTOMY (including division of adhesions releasing obstruction, volvulus, and attempted removal of rectum)	6
CLOSURE OF COLOSTOMY	2
TOTAL NUMBER OF SURGICAL PROCEDURES	90
NUMBER OF PATIENTS OPERATED UPON	50
TOTAL NUMBER OF SURGICAL DEATHS	11
GROSS OPERATIVE MORTALITY	22%

with belladonna and papaverine hydrochloride. If this type can be carried conservatively beyond the stage of acute activity with bleeding, into a more chronic form of the disease, fatalities will be avoided.

Ileostomy is not a difficult or formidable procedure, yet it is one attended with a considerable mortality, eight of our 11 deaths followed ileostomy. Of the 34 ileostomies performed, 22 were elective and 12 were undertaken as emergencies.

The 50 per cent mortality (Table II) in the emergency group is high. Three of the six, however, had perforated before operation, and died from the effects of a preexistent peritonitis.

These patients are admittedly poor surgical risks, regardless of whether one classifies them as acute fulminating, with actual or impending perforation, with or without massive hemorrhage, chronically ill, or intractable and debilitated by inadequate and faulty medical management.

The dread of all surgeons interested in colonic surgery is peritonitis, it is the major cause of death in this disease. Nine of the 11 fatalities in our

series were due to this complication. Three of these cases had perforated before operation was undertaken, two seemed unavoidable, and four were due to technical errors on our part which resulted in peritonitis. In these last four cases, one followed embarrassment to the circulation of a loop of

TABLE II

ILEOSTOMY DEATHS

TYPE OF SURGERY	NUMBER OF CASES	DEATHS	MORTALITY
Ileostomies	34	8	23%
Emergency Ileostomies	12	6	50%
Elective Ileostomies	22	2	9%

ileum which was brought out upon the anterior abdominal wall in an effort to increase the safety factor. Two resulted from dropping back what was thought to be a healthy divided stump of the distal segment of the colon, and the fourth was due to soiling while dividing multiple intra-abdominal fistulae at the time of colectomy.

We highly recommend the technical procedure of forming a mucous fistula in the various steps of the operation. The distal divided end of small or large bowel is thus allowed to remain open on the abdominal wall instead of being sutured and replaced into the peritoneal cavity.

During the past year, in an attempt to obviate peritonitis, we have given sulfanilamide orally as a preoperative medication. At operation, we have poured from 6 to 8 Gm. of the crystalline sulfanilamide into the abdominal cavity prior to closure.

The intra-abdominal application of the drug has been performed in some 50 cases of suppurative appendicitis at the Roosevelt Hospital. The dramatic effect against local abscess and spreading peritonitis, as characterized by the lack of a single death from appendicitis during 1940, prompted us to use the drug in this manner.

We have not attempted, as others have done, to take down an ileostomy and establish an anastomosis between the ileum and lower sigmoid, for fear of a resulting peritonitis or spreading of the disease from the questionably healthy sigmoid into the healthy ileum.

There are other factors which play a rôle in diminishing fatalities following surgery. One of the most important is the accurate evaluation of the

patient's true condition, before operative measures are instituted. In our opinion the most difficult problem is to choose the wisest moment for surgery. Impending perforation is unquestionably an indication.

In the chronically ill individuals there are two groups in which we feel justified to advise surgery: (1) Where there is a progressive and continuous extension of the pathologic changes; (2) Where they continue to have char-

TABLE III

OCTOBER 1 - 1940

MORTALITY FACTORS

NAME	TYPE OF SURGERY	EMERGENCY OR ELECTIVE	REASON FOR SURGERY	CAUSE OF DEATH
C D R	Ileostomy	Emergency	Perforation before operation	Peritonitis
B D	Colectomy	Elective	Intractable	Peritonitis
W E	Ileostomy	Elective	Intractable	Embolism
E H	Colectomy	Elective	Intractable	Peritonitis
F G	Ileostomy	Elective	Intractable	Peritonitis
M H	Ileostomy	Emergency	Impending perforation	Peritonitis Hypoproteinemia
F K	Ileostomy	Emergency	Fulminating	Peritonitis
J M	Colectomy	Elective	Intractable	Peritonitis
J N	Ileostomy	Emergency	Hemorrhage Impending perforation	Paralytic ileus
D R	Ileostomy	Emergency	Perforation before operation	Peritonitis
G S	Ileostomy	Emergency	Perforation before operation	Peritonitis

acteristic periods of recurrence and remission accompanied by an extensive involvement of the colon.

In order to diminish the mortality in the surgical treatment of ulcerative colitis, we cannot emphasize too strongly a meticulous and prolonged medical investigation of these patients. Many abnormal conditions should be corrected before surgery is undertaken. Among them are:

- (1) Active food allergy—the test diet method has proven satisfactory in many instances. These patients do better on a protein diet than on a diet high in carbohydrates, as has hitherto been considered the appropriate “colitis diet.” There has been a variety of foods which have appeared to play a part in the mechanism of this disease, most of these individuals have been allergic to either milk, wheat or eggs. It can be said, with some degree of accuracy, that approximately 50 per cent of the patients indicate that food allergy plays a considerable rôle.

It has been noticeable that no evidence of food sensitization has been demonstrated during the acute stage of the disease, and it has been learned that allergic individuals seem to go through phases of active reactions as well as phases without reaction

It has been emphasized by Mackie¹ that "all patients suffering from this disease should be repeatedly studied in an effort to demonstrate a food allergy mechanism"

- (2) Disturbed physiology of other parts of the digestive tract should be corrected. Gastric anacidity produces diarrhea and flatulence, hypomotility of the colon with right-sided retention contributes to the degree of pain
- (3) Functional diets too low in proteins, thiamin chloride, vitamins A, C and D, and certain members of the B complex
- (4) Anemia should be combated
- (5) Disturbances of mineral metabolism, including calcium, phosphorus or sodium chloride
- (6) General malnutrition and inanition

We believe that adequate and detailed preoperative surgical preparation will assist materially in lowering the mortality. Fluid balance and the blood chemistry can be fairly accurately regulated by daily infusions and transfusions. We know that vitamin C is reduced not only preoperatively but postoperatively. Therefore, these patients are saturated with sufficient vitamin supplements. A nonresidue diet 48 hours prior to the proposed operation helps in keeping the bowel empty, and lead and opium pills and paregoric render the intestine quiescent.

In the earlier group of patients operated upon we used avertin, gas-oxygen-ether as the anesthesia. Lately we have been of the opinion that a spinal anesthesia definitely facilitates the operative maneuver, lessens complications, and is relatively safe. We prefer to use the Howard-Jones solution of nupercaine in 1-1500 dilution with 0.5 per cent saline. To protect these patients against psychic trauma, they are given three nembutal tablets orally two hours before the time of operation, followed in one hour by morphine grains 1/6-1/8 with scopolamine grains 1/150-1/200 hypodermatically. Many of these patients doze throughout the operation and often have little memory of their surgical experience. Fifteen minutes before being brought to the operating room, the patient receives an intramuscular injection of ephedrine, 50 mg, to assist in maintaining the blood pressure.

Spinal puncture is made with the patient in the horizontal position, and the head of the table slightly elevated. The second lumbar space is usually chosen, in order to obtain sufficiently high anesthesia. The dose is varied from 14 to 19 cc, depending on the height and general condition of the patient. Those individuals of short stature, of about five feet three inches, or patients whose resistance has been lowered by the disease receive a smaller dose. The solution is injected slowly. Nupercaine solution is lower in specific

gravity than the spinal fluid, so the patient is immediately turned to the prone position to obtain satisfactory anesthesia of the posterior sensory roots

An infusion of saline solution or saline and glucose is started at the time that the incision is made. This, we believe, is helpful in preventing any serious fall in blood pressure. Should the patient become restless we have not hesitated in supplementing the spinal anesthesia with inhalations of nitrous oxide. Oxygen inhalations are administered at intervals throughout the operation, particularly if there are signs of nausea, color change, respiratory disturbances or fallen blood pressure.

TABLE IV

SURGICAL MORTALITY

PROCEDURES	NUMBER OF CASES	DEATHS	MORTALITY PERCENTAGE
Ileostomy	34	8	23%
Colectomy			
Subtotal	24	2	8%
Partial	7	1	14%
Ileo-sigmoidostomy	6	0	0
Combined Abdomino-perineal resection	7	0	0

When the disease has involved the entire colon, a three-stage operation, we believe, has proven safest. First, ileostomy, second, subtotal colectomy, third, proctectomy. In the proximal type, where the cecum, ascending and transverse colons are involved, ileosigmoidostomy (end-to-side), with the distal divided end of the ileum brought out as a mucous fistula, has proven eminently satisfactory in our hands.

In that group where the disease has invaded only the rectum and the descending colon, transverse colostomy with the removal of the descending colon as a first-stage, and removal of the rectum as a second-stage, has been successful except in one instance, and that fatality was due to an error in judgment, by attempting to close over the distal divided end of the sigmoid and dropping it back in the peritoneal cavity at the first-stage.

Careful postoperative management, especially following ileostomy, is considered of more vital importance than after the other two stages. In order to insure the immediate functioning of the small bowel through the newly made ileostomy stoma, adequate fluids are administered by venoclysis. The chloride and calcium content of the blood, as well as the serum protein are

checked and an attempt is made to keep up these constituents to a normal level. To maintain the chemical balance, the determination in both plasma and serum is helpful.

Administration of thiamin chloride after operation improves the appetite. These patients are thus more easily coaxed into eating early. In order that the ileal stoma may function almost immediately after operation, we feed them almost immediately after their return from the operation. Chewing gum, melba toast, crackers and cracked ice the day of operation seem to start the ileostomy drainage. A soft, low residue diet in small feedings is given every three hours beginning the afternoon of operation. The second day postoperative, a soft diet with copious amounts of fluids is given, and on the third day, a solid diet is permitted.

Beneficial results of this early feeding are (1) The ileostomy stoma begins functioning from 12 to 24 hours after operation. (2) There is a minimum amount of postoperative gas and distention and so the risk of vomiting and ileus is minimized. (3) The weight is maintained and thus the usual convalescent weight loss is rarely more than three to five pounds.

CONCLUSIONS

Radical surgery has proven justified in the treatment of intractable ulcerative colitis. The primary mortality factor, in our opinion, is that surgery is offered too late. Hemorrhage and peritonitis are dreaded complications of this disease, and those patients who have hemorrhages are best treated by medical management. Let us emphasize the importance of a prolonged and careful medical investigation, and urge that the surgeon see the patient during this time of preoperative medical study.

Ileostomy is associated with a higher mortality than are the other procedures, such as subtotal colectomy and proctectomy.

Oral sulfanilamide, preoperatively, and placed into the peritoneal cavity in the form of crystals at the time of operation has been helpful in reducing the mortality.

The externalization of the distal divided end of the small bowel as a mucous fistula after ileostomy is justified as a technical procedure, this also applies to the treatment of the distal divided end of the sigmoid after subtotal colectomy. It is a maneuver that prevents a "blow-out" of the sutured stump, thereby averting peritonitis.

REFERENCE

- ¹ Mackie, T. T. Jour Amer Diet Assn 14, No 3, March, 1938

DISCUSSION —DR FRANK H. LAHEY (Boston, Mass.) This is one of the subjects, I am very certain, that needs frequent discussion, and is a subject, it seems to me, wherein is well-illustrated the value of the combined efforts of the gastro-enterologist, surgeon and the internist, as is true of thyroid disease. Doctor Cave has associated with him Doctor Mackie, who is also interested in the subject, and, thus, it makes an ideal set-up. It is a dangerous disease because of the limited number of cases occurring in any one man's hands.

except those who have a particular interest in it, and the price of acquiring experience is an extremely high mortality. Therefore, it is very desirable that everyone who is dealing with this type of patient, to any great extent, should bring their experience before us.

Doctor Cattell and members of the Gastro-enterologic Department of the clinic, have been much interested in the subject of ulcerative colitis, particularly during the past ten years. Operative treatment has been necessary in a considerable number of these patients, due to complications of the disease, and I should like to present our surgical experience. We have had 280 patients with ulcerative colitis, and in this total group, 80 ileostomies were performed, with a mortality of 20 per cent. Further, in this group of 80 cases, 43 total colectomies, an operation which includes the removal of the rectum, were carried out in stages, with three operative deaths. In addition, 14 partial colectomies were performed without operative mortality when the ulcerative process was segmental or limited to part of the colon. The high operative mortality following ileostomy is due to the fact that this procedure had been delayed too long, and death in these cases is usually due to perforation of the colon. In five patients the ileostomies have been disconnected, restoring the fecal stream, and these patients have remained well. This procedure is justifiable only after a long period of observation following ileostomy, with complete clinical remission of the disease. Furthermore, two additional findings must be present before it is considered: (1) The proctoscopic findings must be negative, showing complete healing of the mucosa, and (2) the barium enema should demonstrate distensibility and contractility of the colon. The fact that the fecal stream can be restored in a few cases without reactivation of the disease makes us feel that early ileostomy is justifiable before extensive damage occurs to the colon.

There are a few points, I think, which should be brought out and stressed. One is that the mortality in ileostomy, as you see in these statistics, is about 20 per cent. This is due to the fact that medical men and patients do not want to face an ileostomy, but we must all strive to see that ileostomies are not undertaken as late as they frequently are. Medical men and gastro-enterologists do not want ileostomies performed, and quite properly so: (1) Because it is such an undesirable type of enterostomy, (2) because they know that the disease is characterized by remissions, and so put it off with the hope that this will occur. When the patient has a high temperature, is prostrated, and everyone—the patient, his family and the medical men—are all convinced that an ileostomy should be made, it is frequently too late. We must perform ileostomies more often at the time when patients do not want them done, if we are to diminish the mortality percentage which goes so often with this procedure, when it is undertaken late.

We have repeatedly said, never perform an ileostomy of the end-type in the acute stage, that is, with the division of the ends, perform, at this time, only the loop-type of ileostomy. This is an emergency, when the patients are extremely ill, with high temperature and intoxication. If you spend the time, then, dividing the ileum and implanting it at two different levels so that later you can perform a colectomy in the stage of the disease which is acute, you will often have a fatality. A fatality at that time will frequently occur because the wall of the bowel is filled with infected organisms, the mesentery with septic thrombi, and the manipulation consequent to cutting the bowel across will cause peritonitis.

There are some rough but practical rules relative to when to perform an ileostomy. Certainly, any patient who has been through two acute episodes

of ulcerative colitis deserves an ileostomy, and it is dangerous to let him go beyond this point. Following an ileostomy many of these patients are greatly improved, but later have recurrence of fever, the discharge of blood and pus, and tenderness over the colon. This is usually due to reactivation of the bowel and blocking-up of its contents due to cicatrization, contractures and strictures. Certainly, any patient who has had two episodes of elevation of temperature, and blood and pus from the colon after an ileostomy deserves consideration of a total colectomy.

There is no more dangerous operation than ileostomy in terms of possible later complications. Often the abdominal wall about the ileostomy is apt to be digested from the effects of the irritating ileal contents. Therefore, it is extremely important to fix the ileostomy to the parietal peritoneum under the edge of the wound, thus guarding against the possibility of a loosening of the ileostomy from the abdominal wall and its retraction into the abdomen.

We do not agree that every patient with a rigid colon is a candidate for ileostomy and colectomy. We have seen at least a few patients with rigid colons who have gotten on, and are getting on, quite well over a long period of time. We believe that one cannot generalize as to this point, but that each case should be dealt with individually.

We need, more than anything else, to get the mortality rate in this disease down by better cooperation between the medical men who see these cases early, and the surgeons who unfortunately now have to operate upon them so late.

DR HARVEY B. STONE (Baltimore, Md.) I thought it might be of interest to Doctor Cave, and the audience, to tell you that we have tried in a limited number of cases the effect of this new drug, sulfanilyl guanidine, in ulcerative colitis as a therapeutic measure. In these few cases, it is my opinion that it has no value as a curative treatment of the basic disease. One or two of these patients we have been able to follow quite closely. One patient is a member of the Surgical Staff. He had an ileostomy performed about a year ago, and for a number of weeks has had the colon irrigated with sulfanilyl guanidine, and has had repeated proctoscopic examinations made. The mucosa is apparently just as inflamed as before, so that any hope that may have existed as to the curative power of this drug in this disease is not apt to be sustained. I think it will prove very effective as preoperative treatment to cut down the colon group of flora in the bowel and, therefore, to render these dangerous colectomies and ileostomies much less dangerous than they would be without administration of the drug.

There is one other point I would like to mention briefly. I quite agree that if one expects an increased number of patients in whom surgery may lead to a definitive cure of chronic ulcerative colitis, we must perform earlier ileostomies. It is not only the reluctance of the surgeon and the patient to submit to the ileostomy that defers operation, but it is, also, the fact that it is a cyclic disease, and the patient and the doctor constantly live in hope that next week or next month the patient will come out of this stage and go into the quiescent stage—they keep on hoping and defer ileostomy. It seems to me that there is a specific evidence of beginning change in the colon which can be obtained—that is, roentgenographic evidence of increasing rigidity and loss of haustration. When the patient begins to show evidence of change, I think it is likely that he is going into a stage of pathologic development which will not be reversible, and if you expect to establish an ileostomy with the hope of ultimately closing the ileostomy, it must be undertaken early, before irreversible changes occur.

DR HENRY W CAVE (New York City, closing) I should like to bring out two or three points, one, is a factor I believe will reduce the mortality—the type of anesthesia. Up to one year ago we employed general anesthesia, but we find now that spinal anesthesia, nupercaine, will give better anesthesia and expedite the operation. We do not like to hurry, and it is not as necessary in most operative procedures as it used to be. But I believe, in taking out the entire colon in desperately sick people, a certain amount of speed will help reduce the mortality. Formerly, we took off the omentum from the transverse colon and let the transverse colon drop more easily. We have abandoned that. We do not think it necessary. Formerly, we did peritonization of the area by removing the colon, and we have abandoned that. We do not think it necessary.

I should like to emphasize Doctor Lahey's statement that we should not be considered mere artisans in doing this, I know of no other disease where close cooperation is more necessary. We have this Ulcerative Clinic, as it is known. Doctor Mackie is there and I see the cases with him. It is sometimes difficult to refrain from operation, but I think the surgeon should be the one to decide and not let the physician pull him into it. Although we have not done it, I think Doctor Lahey's idea of bringing out a loop on the anterior wall, and nothing else, is a good one in the desperately ill patients. I think his classification of when ileostomy and when colectomy should be undertaken is very clear. It is interesting to hear Doctor Stone say that they used sulfanilyl guanidine and had no results. I personally cannot see how any drug can get into the colonic wall and result in any sort of restoration.

To go back to Doctor Lahey's telling of where he has restored the fecal stream by putting it through the colon. I believe in carefully selected patients, where you are sure the rectum and lower sigmoid is somewhat restored, it might be advisable. Doctor Stone, at the American Surgical Association, brought out a very ingenious idea of performing a type of ileostomy with a pocket in it, and I think that should be given consideration. Further, what he says about the early changes in the colon which may be demonstrated roentgenographically, is significant, and then you make your ileostomy and make it early. I did not agree with him last spring, but I am confident that we have had cases in the early stages where they could have been saved had they had ileostomy earlier.

This paper was read before the Fifty-third Annual Session of the Southern Surgical Association, Hot Springs, Va., December 10, 11, 12, 1940

REGIONAL LYMPHATIC METASTASES OF CARCINOMA OF THE COLON

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A KNOWLEDGE of the incidence and the location of the regional lymphatic metastases from carcinoma primary in the large intestine is essential in the treatment of this disease

This study, similar to one made by us on the regional lymphatic metastases of the rectum,¹ and the stomach,² is based upon the dissection and examination of all the lymph nodes from 46 cases of carcinoma of the large intestine This included the following distribution

TABLE I

Site of Tumor	No of Cases
Cecum	4
Ascending colon	4
Hepatic flexure	3
Transverse colon	9
Splenic flexure	3
Descending colon	3
Sigmoid colon	20
Total	46

The lymph nodes were dissected from each specimen after they had been visualized (Fig 1) with clearing by the Spalteholz method, as modified by Gilchrist and David³ All nodes were examined microscopically and the results charted on a diagram, upon which every node was indicated The presence or absence of regional lymph node metastases were then correlated with (1) The age of the patient, (2) sex, (3) duration of symptoms, (4) gross type of neoplasm, (5) size, (6) circumferential extent, (7) depth of infiltration, (8) microscopic type, and (9) the degree of cellular differentiation

Lymph nodes may be isolated by this method which, because of their smallness, go unnoticed by the usual method of dissection Many large nodes were found to be inflammatory and many small impalpable nodes were found to contain metastatic carcinoma Unless a lymph node was definitely replaced by carcinoma, it was impossible to determine without microscopic section whether it was involved These facts of observation demonstrate clearly that the operative procedure should not be minimized because of the absence of palpable lymph nodes It is in these cases that cure may be obtained if the operation be radical

As a result of this special method of investigation, 28 of the 46 cases studied, or 60.87 per cent, showed evidence of regional lymph node metastases. An average of 52.07 nodes was isolated per specimen. There was an average of 59.4 nodes isolated per specimen in cases having nodal involvement and 41.4 nodes in those without metastases. Of the carcinomata of the right colon, 62.5 per cent showed metastases in comparison to 60 per cent of those of the left colon.

The superiority of this method of determining the presence of regional lymph node metastases is realized when these findings are compared to those of other workers. Craig and MacCarty,⁴ in 1923, studied the incidence of regional lymph node metastases from 100 cases of carcinoma of the cecum by the usual method of dissection. They were able to isolate only 10.25 nodes per specimen, with an incidence of nodal involvement of 32 per cent. Hayes,⁵ in 1921, found an incidence of 37 per cent nodal metastases in carcinoma of the large intestine, excluding the cecum, in which only 14.06 lymph nodes per specimen were isolated. Rankin and Olson,⁶ in 1933, reported an incidence of 34 per cent regional lymph node metastases in 187 cases of carcinoma of the right colon, and only 31 per cent in 260 cases of carcinoma of the left colon.

In 1939, Simpson and Mayo⁷ reported an incidence of 41.4 per cent nodal metastases in 120 patients with carcinoma of the colon. These were distributed as follows:

TABLE II

Site of Tumor	No. of Cases	No. of Cases with Metastases	Percentage
Right colon	28	14	50.0%
Transverse colon	15	6	40.0%
Descending colon	26	12	46.2%
Sigmoid colon	51	15	29.4%
Totals	120	47	Avg 41.4%

The incidence of nodal metastases and the anatomic distribution of our cases are:

TABLE III

Site of Tumor	No. of Cases	No. of Cases with Metastases	Percentage
Cecum	4	3	75%
Ascending colon	4	2	50%
Hepatic flexure	3	1	33.3%
Transverse colon	9	7	77.7%
Splenic flexure	3	2	66.6%
Descending colon	3	2	66.6%
Sigmoid colon	20	11	55.0%
Totals	46	28	Avg 60.87%

It is interesting to note that there were three patients with well-differentiated papilliferous adenocarcinomata of only Grade II malignancy, who had small hepatic metastases without demonstrable local regional lymph node involvement.

Regional lymph node metastases is only one factor in determining the operability and prognosis of carcinoma of the large intestine. Inoperability or poor prognosis may result from extensive local infiltration, hematogenous metastases or peritoneal implants. Ten per cent of the neoplasms (five of 46 cases) showed microscopic evidence of infiltration into blood vessels. This figure is slightly less than the incidence of 15 per cent microscopic infiltration of blood vessels noted by us in both carcinomata of the rectum and stomach. These were, in early cases, suitable for operation prior to demonstrable gross

hematogenous metastases. As to local infiltration, 93.1 per cent had completely infiltrated through the bowel wall. This is a constant source of free peritoneal implantation.

Lymphatic Drainage of the Large Intestine—Delamere, Poirier and Cuneo,⁸ and Jamieson and Dobson⁹ were the first thoroughly to investigate the lymphatic drainage of the large intestine. This consists of three systems: The intramural, intermediary, and extramural lymphatic networks.

The intramural system consists of the submucosal, intermuscular and subserosal networks. Where the large intestine is devoid of a continuous longitudinal muscle layer, the intermuscular and subserosal networks are the same. The lymph channels begin about the mucosal glands of Lieberkuhn and drain to the submucosal network. This network communicates freely with similar channels above and below the site of the lesion, but lymph tends to flow toward the deeper intermuscular and subserosal networks. Since lymph channels follow the course of the radial blood vessels around the circumference of the bowel, carcinomata of the large intestine, as well as the rectum tend to be annular. The lymph then flows from the intramuscular system through the intermediary lymph channels to the extramural lymphatic system. This consists of a group of nodes and lymph channels anatomically arranged about the blood vessels and are described by Jamieson and Dobson⁹ as corresponding to these vessels. Thus, there is the ileocolic chain, the right colic chain, the middle colic chain, the left colic chain, and the inferior mesenteric chain. Along each chain, there are aggregations of nodes that are designated as the epicolic, paracolic, intermediate, and the main group of nodes.

The epicolic nodes lie anterior or posterior to the intestinal wall. The paracolic nodes are located upon the medial aspect of the intestine along the vascular arcades and the short terminal vessels leading from the arcades. The intermediate nodes are situated about midway between the arcades and

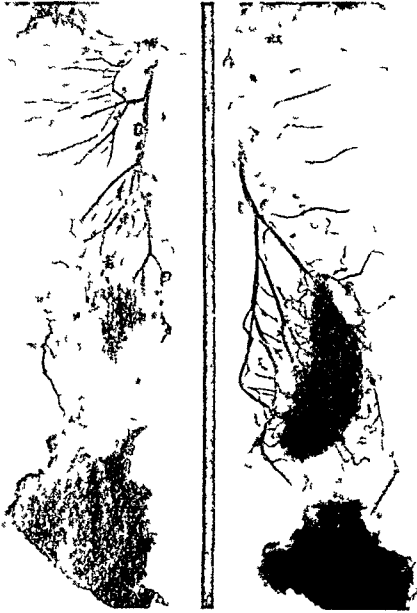


FIG. 1.—Photographs of cleared specimens of carcinoma of the rectum.

METASTASES OF CANCER OF COLON

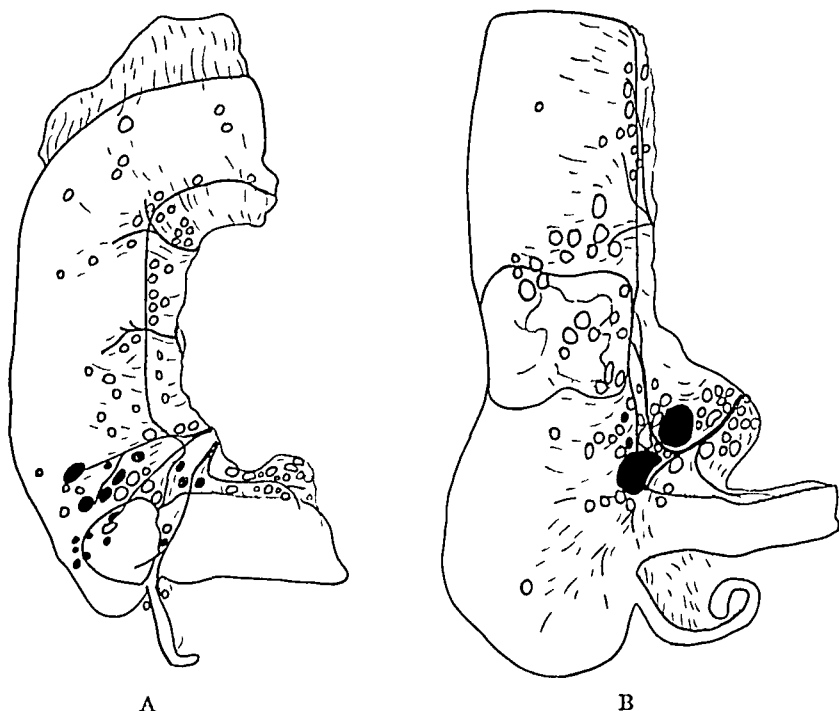


FIG 2—(A) Line drawing illustrating the regional lymphatic metastases along the ileocolic chain from carcinoma of the cecum (B) Line drawing illustrating the downward spread of lymphatic metastases to the ileocolic chain from carcinoma of the ascending colon

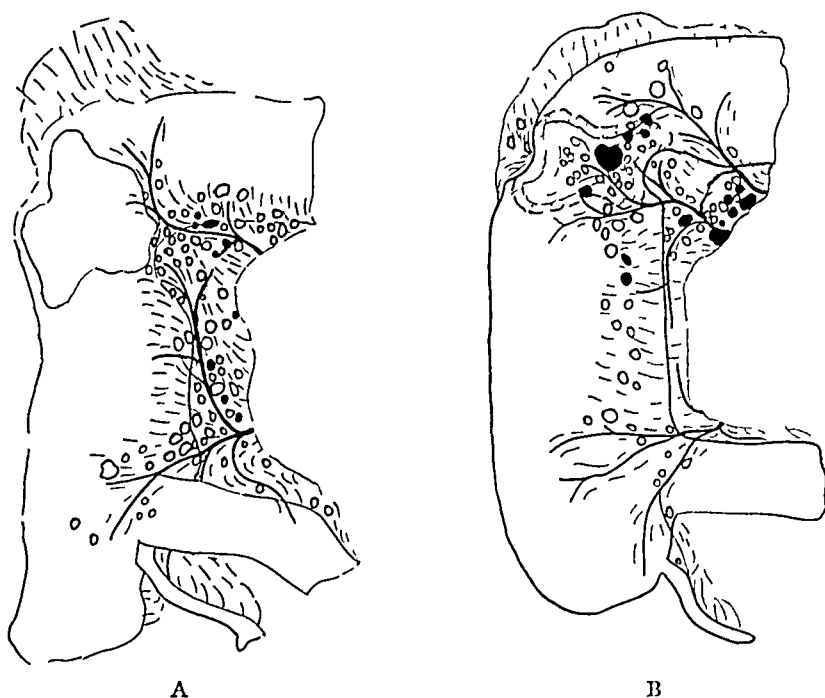


FIG 3—(A) Line drawing illustrating two routes of lymphatic metastases from carcinoma of the hepatic flexure, one downward along the ileocolic chain, the other along the middle colic chain (B) Line drawing illustrating two routes of lymphatic metastases from carcinoma of the hepatic flexure, one along the right colic chain, the other along the middle colic chain

the origins of the ileocolic, colic, or sigmoidal branches, whereas the main group surrounds the stems of the vessels at their origins

The ileocolic route of spread drains the terminal ileum, cecum, appendix and the greater part of the ascending colon. Figure 2 A aptly demonstrates this route of lymph node metastases from carcinoma of the cecum. In Figure 2 B, a carcinoma of the ascending colon, the downward metastases toward the ileocecal junction is well shown.

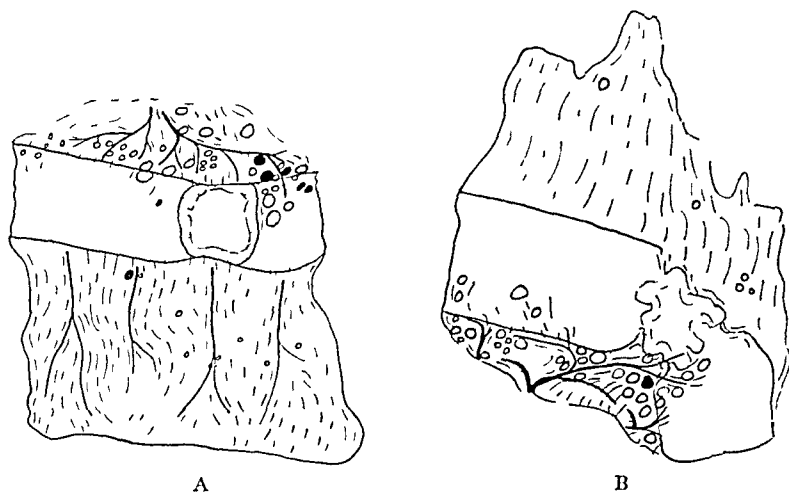


FIG. 4—(A) Line drawing illustrating the regional lymphatic spread along the middle colic chain from carcinoma of the transverse colon and also the metastases of carcinoma of the transverse colon to lymph nodes in the omentum. (B) Line drawing illustrating the regional lymphatic metastases from carcinoma of the splenic flexure.

The right colic chain drains the area supplied by the right colic artery. These nodes are not constant, in that the right colic artery is not constant. They may drain downward into the ileocolic chain, may go medially toward the superior mesenteric nodes, or may drain upward into the middle colic chain. Figure 3 A, demonstrating the lymph node metastases of a carcinoma of the hepatic flexure, illustrates two routes of spread, one downward along the ileocolic chain, and the other passing more medially along the middle colic chain. Whereas, in Figure 3 B the carcinoma of the hepatic flexure appears to be metastasizing by the right colic chain, as well as the middle colic chain, to a lesser extent.

Similarly, the middle colic chain drains the area of distribution of the middle colic artery, that is, the upper part of the ascending colon, hepatic flexure and the proximal two-thirds of the transverse colon. Since the direction of the middle colic artery is to the right, toward the head of the pancreas, in the base of the mesocolon, the spread of metastases is downward and then toward the right. Furthermore, there is a communication between the lymphatics of the transverse colon and those of the omentum, which drain into the nodes along the greater curvature of the stomach. Figure 4 A illustrates this point.

The left colic chain drains the area of distribution of the left colic artery (Fig. 4 B). Neoplasms of the distal one-third to one-half of the transverse

colon would tend to drain toward the left, whereas neoplasms of the upper descending colon might drain either upward toward the splenic flexure (Fig 5 A), or downward toward the sigmoidal vessels (Figs 5 and 6) Lesions of the splenic flexure may spread through lymphatics of the omentum and eventually drain to the splenic lymph nodes

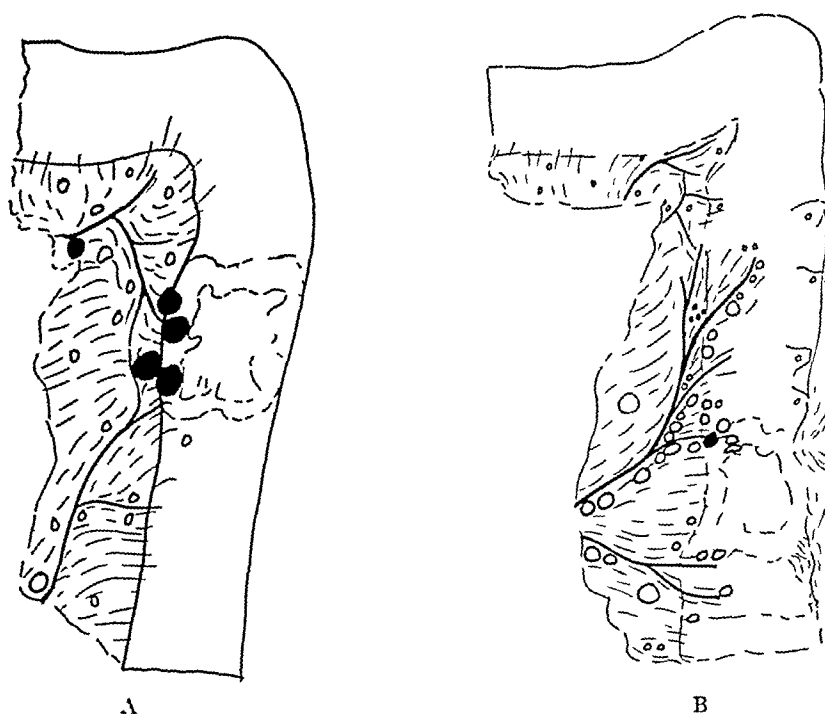


FIG 5 —(A) Line drawing illustrating the upward lymphatic metastasis of carcinoma of the descending colon along the left colic chain (B) Line drawing illustrating the regional lymphatic metastasis of carcinoma of the descending colon along the sigmoidal chain

The inferior mesenteric chain, and specifically the sigmoidal division, drains the area of distribution of the sigmoid vessels Here, the intermediate nodes lie along the sigmoidal vessels, while the main nodes lie along the course of the inferior mesenteric vessels Figures 6 A and 7 show, diagrammatically, the lymph spread of carcinoma of the sigmoid colon, demonstrating metastases to the epicolic, paracolic, and intermediate lymph nodes while a single paracolic metastasis is seen in Figure 6 B

Since it is impossible to determine the presence or absence of regional lymph node metastasis by manual palpation, and since this study has shown that 60.87 per cent of the neoplasms of the large intestine have metastasized to lymph nodes, the surgeon must recognize the necessity of including these areas within the confines of the operative resection, even in the absence of palpable nodes

Lymphatic vessels differ from blood vessels in that instead of one or two channels draining the same area, the lymph is returned by a number of channels which tend to form a plexus about the blood vessels There may also be a number of efferent vessels to any one node, thus explaining the observation that contiguous lymph nodes may not be involved As a rule the epicolic nodes are the first to be involved by metastatic neoplastic emboli However,

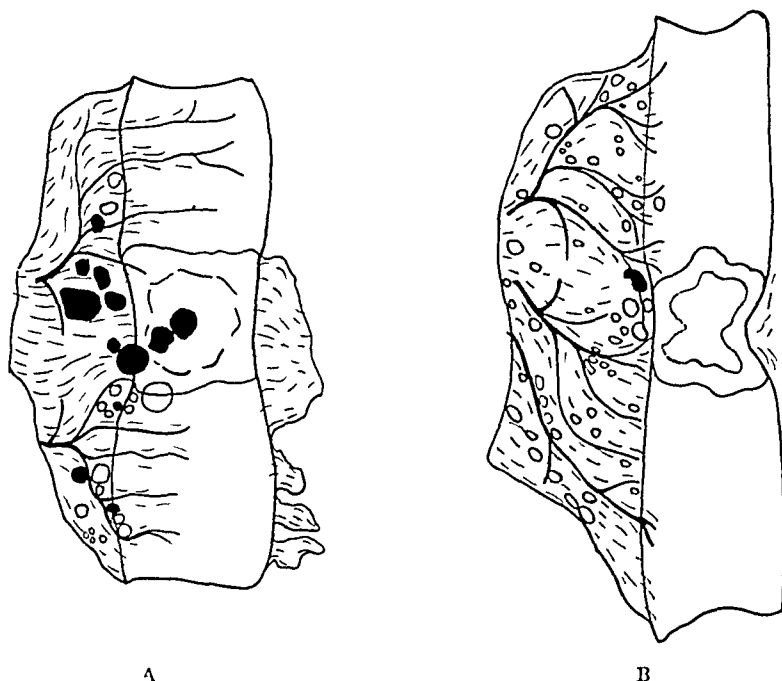


FIG 6—(A) Line drawing illustrating regional lymph node metastases to the epicolic paracolic and intermediate lymph nodes of the sigmoidal chain from carcinoma of the sigmoid colon (B) Line drawing illustrating the singular regional paracolic metastasis from carcinoma of the sigmoid colon

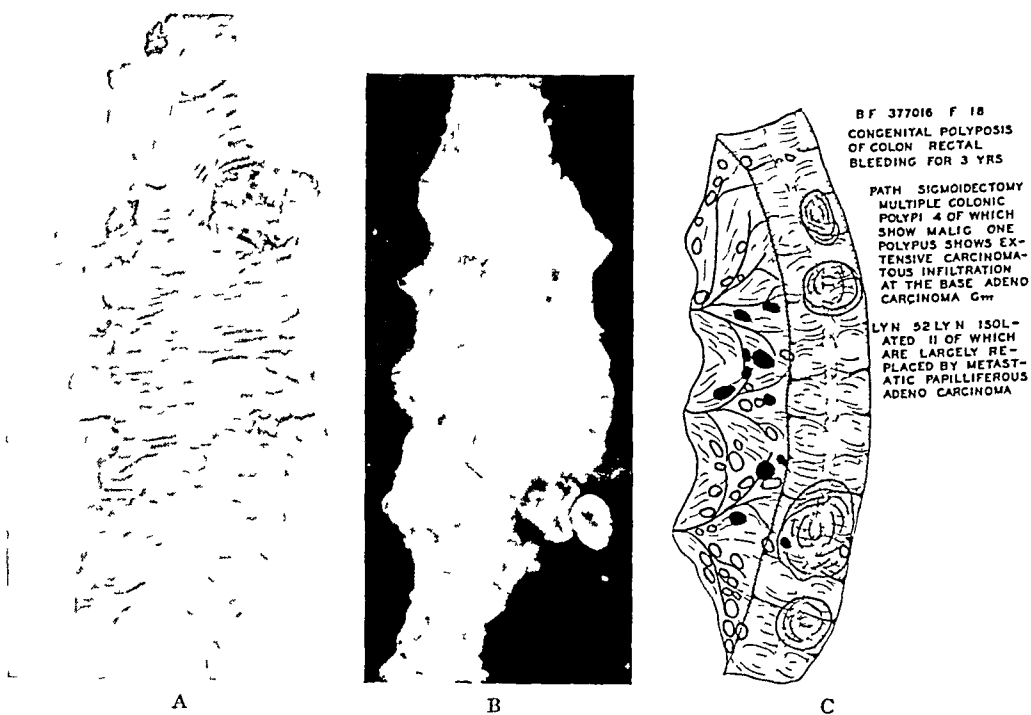


FIG 7—(A) Photograph of gross specimen of sigmoid colon illustrating polyposis of the colon in which four of the polyps had undergone malignant proliferation (B) Photograph of cleared specimen shown in Figure 7 A (C) Line drawing illustrating the regional lymph node metastases from carcinoma of sigmoid colon demonstrated in Figure 7 A

often the neoplastic embolus is contained within a lymph channel that drains directly to either the paracolic or intermediate nodes without primary epicolic lymph node involvement. Lymph nodes act as barriers to filter out neoplastic emboli. A neoplastic embolus enters a lymph node by its peri- and subcapsular lymph channels. If the metastasis remains viable, it sets up a new neoplastic focus, tending to block the lymph channel, which then becomes dilated and

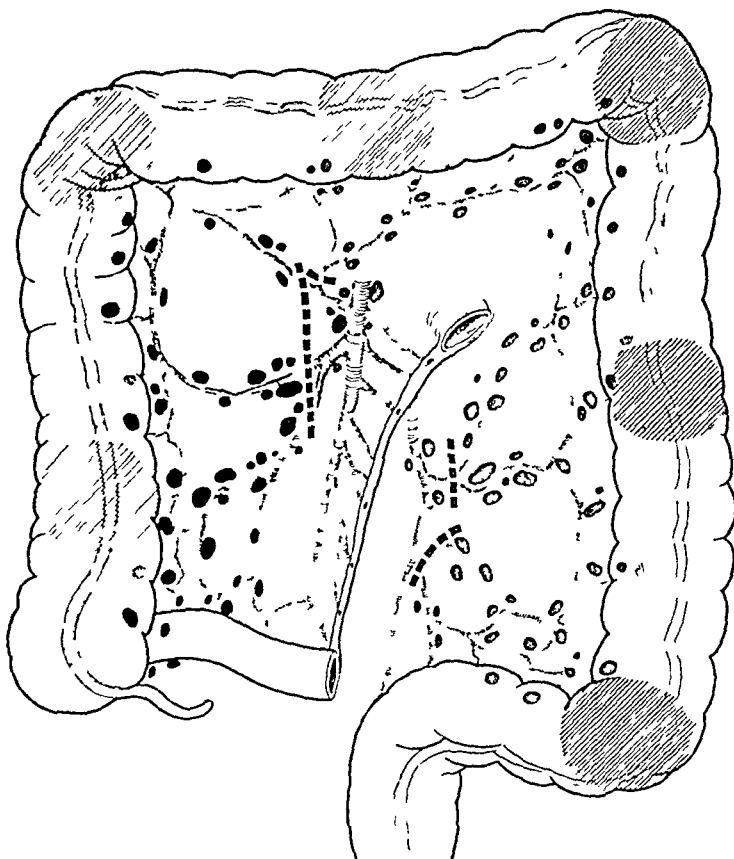


FIG 8—Diagrammatic drawing illustrating the lymphatic metastases from carcinoma of the colon. The dotted lines represent the ideal lines of section of the mesocolon to include the possible epicolic, paracolic, and intermediate lymph node metastases.

distended with lymphocytes. Lymph flow becomes static and other neoplastic foci are often established along the course of the lymph channels. The direction of lymph flow determines the direction of lymphatic metastases. If the lymph channels become plugged with neoplastic emboli, then the lymph will find unobstructed channels and neoplastic emboli may metastasize along other zones of spread.

Figure 8 summarizes, diagrammatically, the lymphatic drainage of the large intestine. The surgeon should include within the confines of the resection not only the primary growth but also its epicolic, paracolic and intermediate nodes of lymph drainage. If the carcinoma has metastasized to the main group of lymph nodes at the origins of the various vessels, then generalized metastases, undoubtedly, have already occurred, and any operative procedure would only be palliative in character. In Figure 8, the dotted lines represent the ideal

lines of section of the mesocolon for the various sites of carcinoma of the large intestine and simply restate the original suggestions of Jamieson and Dobson.⁹

Age and Metastases—The average age of patients with metastases was 50.9 years, in comparison to 59.1 years in those without. There were two cases 18 years of age, a brother and sister, both of whom had polyposis of the colon, with multiple areas of carcinomatous proliferation (Fig. 7). Although these carcinomata were graded II and III, there was evidence of early hepatic metastases at the time of operation. Since both patients were obstructed, resections were performed, and the bowel continuity restored. The third youngest patient, a male, age 27, also had lymph node metastases. There were eight patients 67 years of age or over, five of whom (62.5 per cent) had metastases. Seventy-five per cent of the patients (nine of 12 cases), 50 years of age or below, had metastasized, in comparison to 55.8 per cent of the patients (19 of 34 cases) above 50 years of age. This substantiates the view that prognosis is less favorable in the younger age-groups than the older.

Sex and Metastases—There was no essential difference between sex and the presence of lymph node metastases. Sixty-one point nine per cent of the male patients (13 of 21 cases) had nodal involvement, in comparison to 60 per cent (15 of 25 cases) of the female patients.

Duration and Metastases—It was noted that the patient with a short duration of symptoms did not always have as favorable a prognosis as the patient who had had symptoms for a longer period of time. In the groups, as a whole, there was an average duration of 10.4 months in patients having regional lymph node metastases, as compared to an average of 11.5 months in those without. In analyzing the data further, there was an incidence of only 40 per cent metastases (four of ten cases) in patients who had had symptoms for two years or more, in contrast to an incidence of 73 per cent metastases (eight of 11 cases) in patients with symptoms of three months or less. This emphasizes the fact that many patients with symptoms of long duration and who are still operable often have the best prognosis, in that the neoplasm is slowly growing and of low malignancy. These apparent discrepancies are explained by the fact that only lesions that were resected could be studied and all inoperable lesions are thus, automatically, excluded from the study.

Gross Types and Metastases—The carcinomata of the large intestine were classified into two groups, the polypoid and the sessile. The classification was based entirely upon whether the neoplasms tended to be bulky and to grow out into the lumen (polypoid) or whether they were plaque-like and tended to infiltrate—to be invasive (sessile). The other gross characteristics, such as stenosing, annular, constricting, and ulcerating, we did not feel to be of any clinical value in determining prognosis or likelihood of metastases. It is frequently stated that carcinomata of the right half of the colon are large, ulcerating, fungating, polypoid carcinomata and that those of the left colon are small, annular, stenosing, scirrhous carcinomata. Differences in the gross characteristics of these neoplasms are not the result of any inherent factor within the neoplasm itself to assume these forms, but rather are the result of

the location in which they are found. The caliber of the right colon is considerably larger than that of the left colon, consequently a neoplasm will have acquired a larger size in the right colon than the left before symptoms referable to its presence are made known. There were as many polypoid carcinomata of the left colon as of the right colon, and in all cases there was evidence of ulceration. Twenty of the 13 carcinomata of the sigmoid flexure were stenosing in character—one in the ascending colon, two in the hepatic flexure, four in the transverse colon, three in the splenic flexure, and three in the descending colon. None of these carcinomata was shown, microscopically, to be scirrhus in character. As to the correlation between gross type and regional lymph node metastases, 57.5 per cent of the polypoid neoplasms (23 of 40 cases) had metastasized, in comparison to 83.3 per cent of the sessile neoplasms (five of six cases), demonstrating the more benign character of the polypoid growths.

Size and Metastases—It has been mentioned that the group with metastases had given symptoms a shorter time than those without. It is of interest to note that the incidence of metastases is higher in the smaller lesions than in the larger. In order to arrive at a more accurate figure as to the size of the neoplasm, its area rather than any one diameter was used. The average size of carcinomata of the right colon with metastases was 32.75 sq. cm., in comparison to those without metastases, in which the neoplasms averaged 39.5 sq. cm. Similarly, the average size of neoplasms of the left colon with metastases was 22.11 sq. cm., in comparison to 31.73 sq. cm. in those without metastases. Thus, we see that the neoplasms in which nodal involvement occurred were definitely smaller than those in which there were none, indicating that the smaller neoplasms giving rise to symptoms were more malignant in character and metastasized sooner. Furthermore, it is noted that the neoplasms of the right colon are considerably larger than those of the left. The largest neoplasms of the entire group were those located in the cecum, these averaged 46.56 sq. cm. in size—accountable by the fact that the caliber of the lumen of the cecum is the largest in size.

Circumference Involved and Metastases—In no case was there less than 25 per cent of the circumference involved. The majority of the neoplasms (37 of 46) were completely annular. In only three instances had the carcinomata involved less than 50 per cent of the lumen and, in three cases, had involved less than 75 per cent of the lumen. The remaining three cases were included in the group having from 75 to 100 per cent circumferential involvement. Because of the large incidence of completely annular carcinomata, the correlation between circumferential involvement and metastases is not striking. It is noted, however, that of the three cases in which between 25 to 50 per cent of the circumference was involved, only one had metastasized.

Depth of Infiltration and Metastases—As might be expected from these observations, in which 40 of the 46 carcinomata were either completely annular or found to involve over 75 per cent of the bowel circumference, and had also attained large size before symptoms were produced, in all but three cases the neoplasm had completely infiltrated through the bowel wall. Of the three

infiltrating only partially through the musculature, two had already metastasized. Consequently, any attempt at correlation of depth of infiltration and the presence of lymph node metastases is futile.

Degree of Cellular Differentiation and Metastases—The preponderance of the carcinomata were graded II as to cellular differentiation. This included 36 of the 46 patients. There were nine neoplasms graded III, and only one graded IV. There were no Grade I carcinomata in our series. As shown in Table IV, the incidence of lymph node metastases was directly proportional to the degree of cellular differentiation.

TABLE IV
DEGREE OF CELLULAR DIFFERENTIATION AND METASTASES

	Grade	No of Cases	No with Metastases	Percentage
II		36	21	58.3%
III		9	6	66.6%
IV		1	1	100%
Totals		46	28	

Microscopic Type and Metastases—The majority of the carcinomata were found, histologically, to be simple adenocarcinomata. These composed 29 of the 46 cases. The papilliferous adenocarcinomata had the smallest incidence of nodal involvement. These metastasized in only 37 per cent of the cases. The medullary adenocarcinomata had the highest incidence of metastases, and metastasized in 80 per cent of the cases. The second highest incidence was noted in the adenocarcinoma mucosum. Table V designates the number and incidence of the various histologic types with metastases.

TABLE V
HISTOLOGIC TYPE AND METASTASES

	Histologic Type	No of Cases	No with Metastases	Percentage
Papilliferous adenocarcinoma		8	3	37.5%
Adenocarcinoma (simplex)		29	18	62.07%
Adenocarcinoma mucosum		4	3	75.0%
Medullary adenocarcinoma		5	4	80.0%
Totals		46	28	

SUMMARY AND CONCLUSIONS

A study of the lymph nodes in 46 specimens of carcinoma of the colon was made by David and Gilchrist's modification of the method of Spalteholz. An average of 52 nodes were isolated per specimen. These were examined microscopically and charted on diagrams. Sixty point eighty-seven per cent of the specimens showed evidence of involvement of the lymph nodes by metastases. There was an average of 59.4 nodes isolated per specimen in those showing nodal involvement, and 41.4 nodes isolated in specimens showing no metastases. Sixty-two point five per cent of carcinomata of the right colon showed metastases, in comparison to 60 per cent of those of the left colon.

The routes of spread of carcinoma by the lymph channels are discussed

Size of nodes is not an index of metastatic involvement Duration of disease and size of tumor are not correlative with extent of nodal involvement

Operation for removal of carcinoma of the colon should be planned on an anatomic basis, so as to include lymph node-bearing areas rather than on palpability of lymph nodes The presence of metastases in lymph nodes from carcinoma of the colon is more frequent than indicated by previous studies based on isolation of lymph nodes by gross methods of dissection

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This paper was presented before the Fifty-third Annual Session of the Southern Surgical Association, Hot Springs, Va, December 12, 1940

RECURRENT CARCINOMA OF THE RECTUM

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Case Report—In November, 1924, a male, age 26, was referred to the Johnston-Willis Hospital for study. Two years ago, in 1922, the patient had first noticed blood on defecation. For about a year thereafter his condition showed little change, but, in 1923, he began to feel that there was some obstruction low down in his abdomen, and that his bowel movements were incomplete. Occasional laxatives failed to relieve him. He resorted to enemata about three times a week, which afforded temporary relief. He became nervous, but slept well, had an excellent appetite, no nausea or vomiting, and no abdominal pains except when enemata were not employed. He had lost about ten pounds during the past year.

He consulted his family physician early in the fall of 1924, complaining only of the rectal bleeding and the constipation, which had increased over the past 15 months.

This patient's family history was significant. A brother died of carcinoma of the stomach at age 27, his grandfather died of carcinoma of the rectum. In 1919, the patient had an infected ulcer on his leg which lasted six weeks. No specific treatment was administered.

Laboratory Data—Repeated Wassermanns were negative, spinal fluid, negative, hemoglobin, 68 per cent.

A barium enema showed an annular filling defect in the rectum, within seven centimeters of the anus. The defect itself was about three centimeters long and the caliber of the rectum was obliterated to a diameter not much larger than that of a lead pencil.

Complementing the roentgenologist's report, the findings of digital and proctoscopic examinations converged on a diagnosis of carcinoma of the rectum. The diagnosis was confirmed by biopsy.

On November 21, 1924, a Kraske resection of the rectum was performed. The dissection was extended into the peritoneum. The peritoneal cavity was opened anteriorly, and the entire rectum with adjacent nodes was removed. The growth was reported to be a carcinoma Grade II, with involvement of adjacent nodes (Fig. 1).

The patient was discharged from the hospital six weeks after operation. Because of his age, only 26, and the malignant involvement of his nodes, I kept in touch with this case for a number of years. His functional results were reasonably good. He continued in business as a successful architect, was married in 1928, and has a daughter now nine years old.

In November last year, he was referred to me again for treatment of what his surgeon thought to be a liberal redundancy about the stoma. A local examination and biopsy proved this to be a carcinoma of much the same type as previously reported. After the necessary preparations, the patient was operated upon again, December 11, 1939. A combined abdominal and posterior resection was completed in one stage. Some difficulty was encountered because of scar tissue from the former operation. However, the patient stood the operation well.

A troublesome ileus developed during the convalescence, but use of our weighted Miller-Abbott tube saved him from an enterostomy, and enabled the patient to make a complete operative recovery.

This time, the pathologic report showed that both the growth and the nodes were adenocarcinoma, Grade III.

Certainly, the above case report presents nothing original or new in symptoms or surgery. The symptoms are classic, the treatment standard. Instead

of the former operation carried out for resection of the rectum, a combined abdominoperineal resection, for a good surgical risk, would be our choice to-day. The writer feels, however, that an abdominoperineal resection in 1924 would hardly have changed the outcome in this case. Our real interest lies

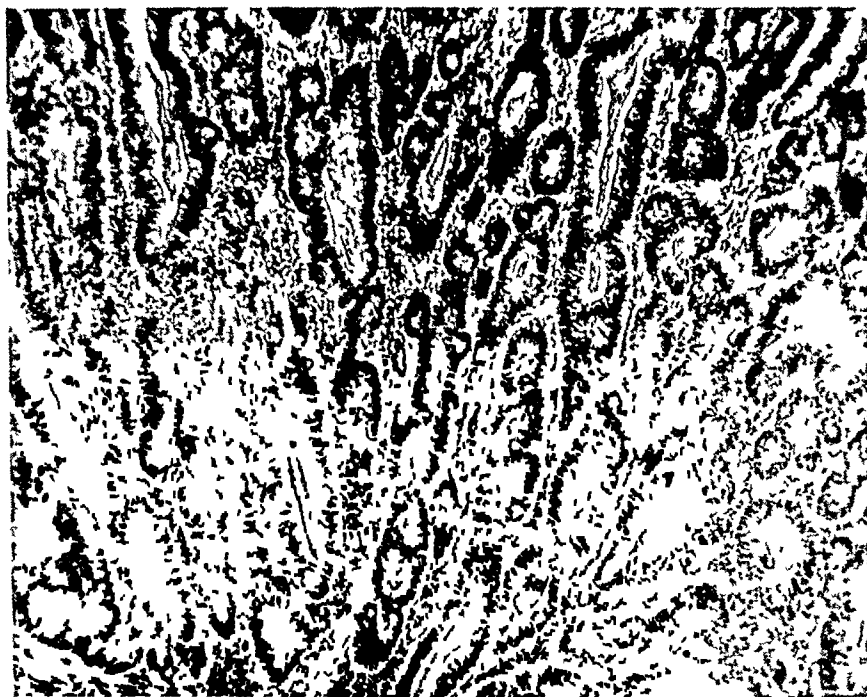


FIG 1—Photomicrograph of tumor removed November 21, 1924. Diagnosis Adenocarcinoma of rectum—Grade II

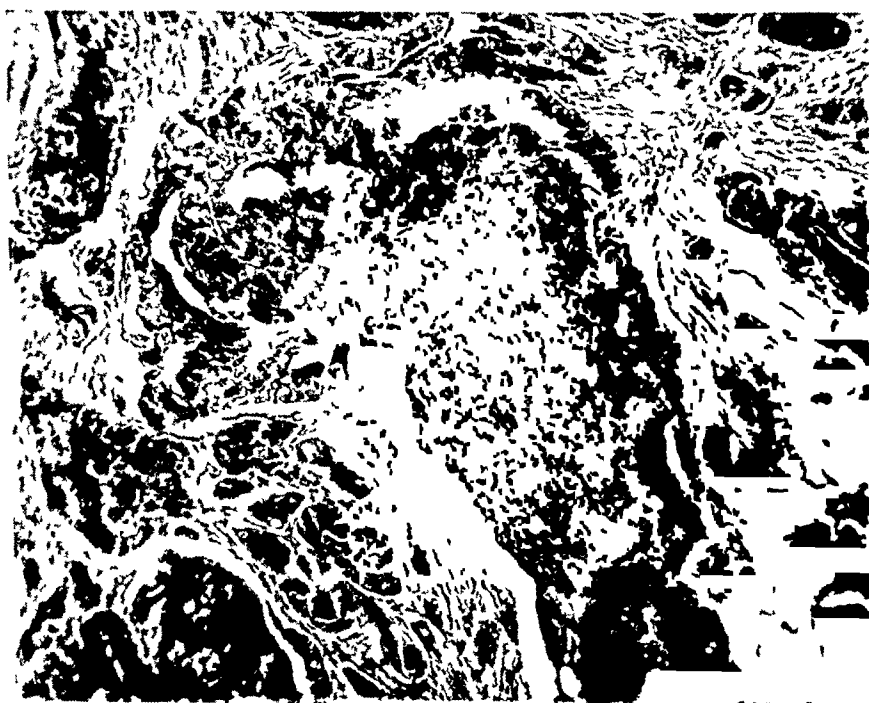


FIG 2—Photomicrograph (low power) of the recurrent tumor. Removed December 11, 1939. Diagnosis Adenocarcinoma of rectum—Grade III

in the fact that so young a man remained active and well for more than 15 years after the removal of a carcinoma Grade II with lymph node involvement, but was then found to have an operable recurrence of a similar type of adenocarcinoma with the same lymph node involvement. Although more

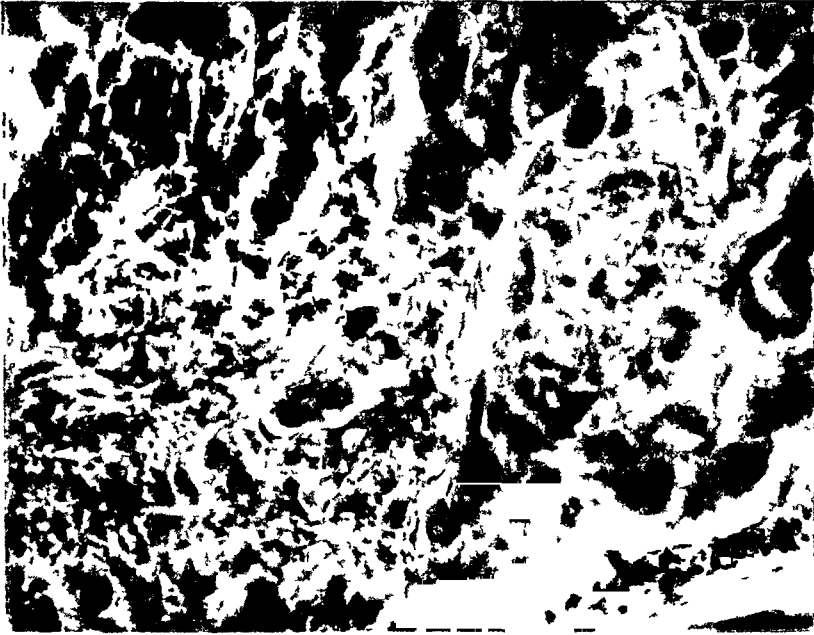


FIG 3—Photomicrograph (high power) of Figure 2 showing hyperchromatic nuclei with an abundant cytoplasm, and mitotic figures

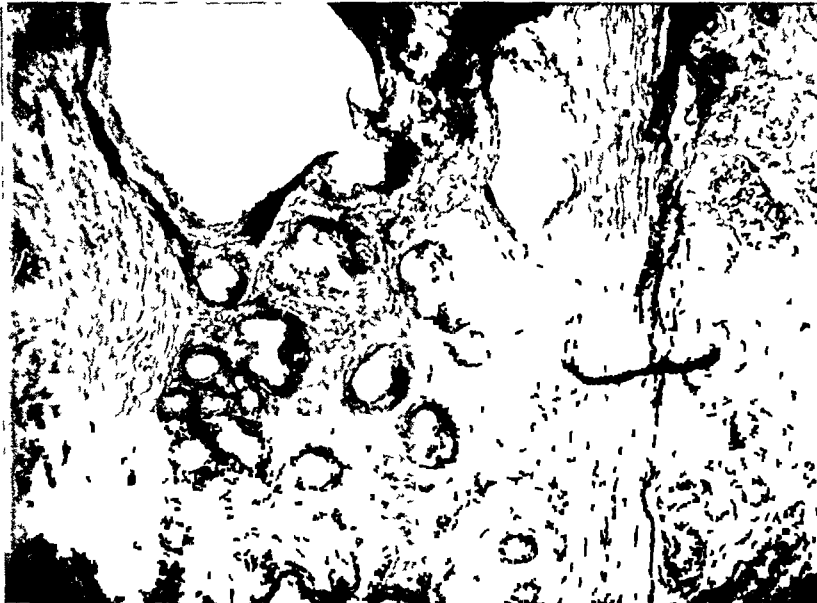


FIG 4—Photomicrograph (low power) showing normal and abnormal sweat glands

than 15 years had elapsed since his primary malignancy, we have classed this case as "a recurrence" At his second operation, the patient presented nearly the same type of lesion, the pathologist reported "a striking resemblance in the cell morphology to the previous growth, and that this was probably of similar cell origin"

Not much parallel is to be read, or information had, on this condition References to operable "recurrence" are scant in cancer literature Jerome M Lynch¹ in an interesting case-report says "I operated upon Miss G in 1926, performing a combined abdominoperineal operation with a perineal stoma I excised 25 cm of the lower bowel, including the anus The growth (Broders Grade II) was found to begin 4 cm above the anal verge, and to extend 5 cm

"There was also a chronic inflammation of the lymph nodes Two years later, there was a recurrence of the disease It consisted of two separate growths, both of which were Grade III, more malignant than the primary lesion I must say that it was with some misgivings that I undertook to operate a second time Seven years have elapsed since the second operation, and the family tells me she is the most cheerful person in the neighborhood and one of the most active"

In Lynch's case, it should be noted that the lymph nodes were inflammatory, not malignant But within two years there was a recurrence of the carcinoma It is also notable that this patient had remained well for seven years after her second operation for cancer

Richard B Cattell states that in the presence of a recurrence, roentgen ray and radium therapy definitely increase the duration of life and contribute to the patient's comfort He makes no reference to further surgery From this and other reports in the literature, the accepted treatment for recurrence in carcinoma is not surgical The preponderance of evidence is in favor of radium and roentgenotherapy

We fully realized, at our patient's first operation, that a 26-year-old man, with gross symptoms of more than two years' duration, stood a good chance for a cancer recurrence We were especially concerned after the lymph nodes about the rectum were found to be of the same grade malignancy At the end of five years he reported for examination A thorough check-up failed to show any irregularity He was married, had one child, was successful in business, and enjoying good health Ten years passed, and he reported continuing good health When he reported himself well after 15 years, we really discharged him as a "cancer cure"

We learned, during the sixteenth year of his recovery, that he was having trouble again, but we supposed, of course, that it would be from an irritated, redundant perineal stoma However, on his arrival for examination, we realized at once that he had a local recurrence of carcinoma of the stoma Upon further examination we found that, this time, the growth extended about 7 cm above the stoma

After removing this growth, we were impressed to learn that the path-

ology from the bowel and lymph nodes were strikingly similar to that from the former operation, except that these were found slightly more malignant than the tissues removed 15 years previously

One year has now elapsed since our second operation upon this case of recurrent carcinoma of the rectum. He has been active again in his business, and on examination a few days ago, he seemed to be in good health. But our experience with this patient somewhat dampens any attempt to declare a cure in the case of cancer.

REFERENCE

¹ Lynch, Jerome M. N. Y. Surg. Jour., 38, 268-273, February 15, 1938

This paper was read before the Fifty-third Annual Session of the Southern Surgical Association, Hot Springs, Va., December 10, 11, 12, 1940

RESULTS WITH THE FASCIA PLASTIC OPERATION FOR ANAL INCONTINENCE

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BALTIMORE, M.D.

ABOUT 12 YEARS AGO one of the present writers¹ presented to the Southern Surgical Association a method for restoration of control of the anal outlet, which was based upon an original idea of the Russian orthopedic surgeon, R. R. Wieden.² A few years later, he published two other papers,^{3, 4} relating further experience, and modifying somewhat the technic of the operation. Since then there has been no change in the essential technic, but considerable additional experience with its employment has accumulated, and, also, time has permitted a study of the late results. It seemed to us that a report of such a study would provide a basis for estimating the value of the operation.

A brief résumé of the operative steps is perhaps indicated. With the patient in the lithotomy position, the usual surgical clean-up is carried out. This will be much more effective, and the operative success made more probable if the patient has been prepared for several days previously with a low residue diet and daily measures to empty and cleanse the colon.

Two small incisions are placed symmetrically on either side, parallel to the line joining the tip of the coccyx to the tuberosity of the ischium, and about 2 cm. posterior to the anal margin. These wounds are deepened bluntly into the subcutaneous fat. Then, by blunt dissection a curved Kelly clamp is pushed from one incision to the other, in front of the rectum, in the subcutaneous fat, care being taken to avoid injury to the rectum, anal canal, or vagina. The clamp is then opened and is made to grasp and lock on the ends of two strips of fascia at least 12 to 15 cm. long and about 0.5 cm. wide. This fascia may be either autogenous from the patient's thigh, or prepared sterile ox fascia. We think one gives as good results as the other in this particular operation, and, hence, usually employ the more easily obtainable ox fascia. The clamp holding the strips of fascia is now pulled back through the tunnel that it has made, which thus places two fascia strips in front of the anal canal, in the subcutaneous tissues. A Kelly clamp then is pushed, in similar fashion, from one incision to the other in the subcutaneous tissue behind the anus, and carries with it the end of one of the fascia strips from the first incision to the second. This end is drawn out of the second incision, so that this strip enters one incision, encircles the anus under the skin and emerges from the same incision. Before the clamp is drawn back, it grasps the end of the other strip. It is then withdrawn, pulling this second strip with it. Thus, the second strip also encircles the anus, but from the opposite side and its two ends emerge from the opposite incision. The finger is then inserted into one of the incisions and feels outward and backward until the mesial

margin of the gluteus maximus is defined. An aneurysm needle or clamp carrying a strong guide thread is then pushed around a substantial bundle of the gluteus muscle. This thread is tied to one of the ends of fascia lying in the incision, which is then pulled around the bundle of gluteus fibers

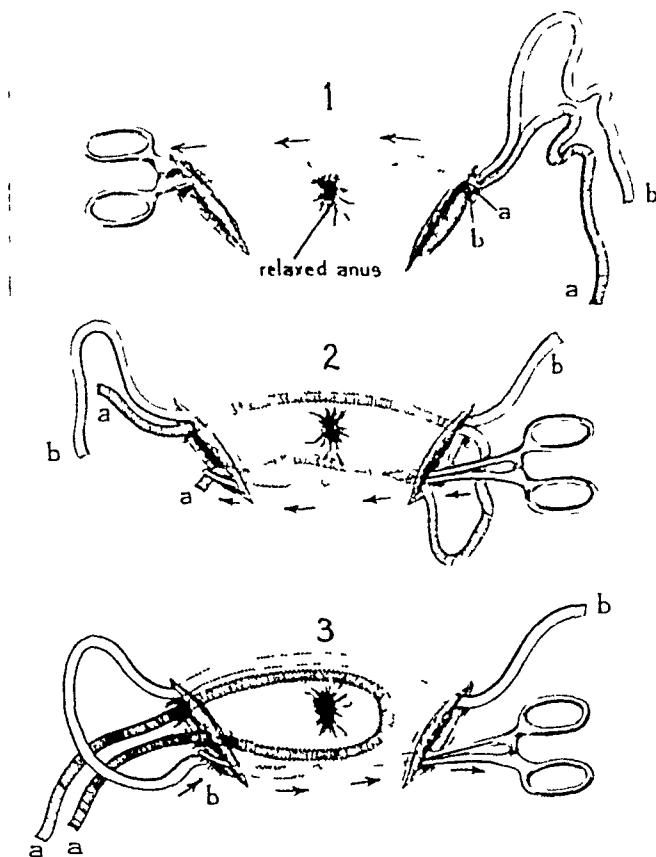


FIG 1—Steps in the plastic operation for anal incontinence. (1) Clamps are passed subcutaneously in front of the anus grasping the strips of fascia and are about to be pulled from one side to the other. (2) Both strips are passed subcutaneously in front of the anus and one posteriorly. (3) The loops of fascia encircle the anus subcutaneously in opposite directions. (Arch Surg, 24: 123, 1932)

This end of the strip is then tied to the other end of the same fascia strip, in a firm square knot, with enough tension to close the anal opening snugly, but not with strangulating tightness. A similar maneuver is carried out on the other side. Thus, the two fascia strips form closed rings which encircle the anal canal on their inner or mesial curves, and a bundle of gluteus fibers on their outer curves, but pull against each other and firmly close the anal canal. These steps are shown in Figures 1, 2 and 3.

Thirty cases, operated upon by six surgeons, have been reviewed. The data concerning these cases were derived from the records of the Johns Hopkins Hospital, the Union Memorial Hospital, and the Church Home and Infirmary.

It is worth while to note that all of these patients suffered from a degree of incontinence severe enough to cause them to seek surgical treatment for its

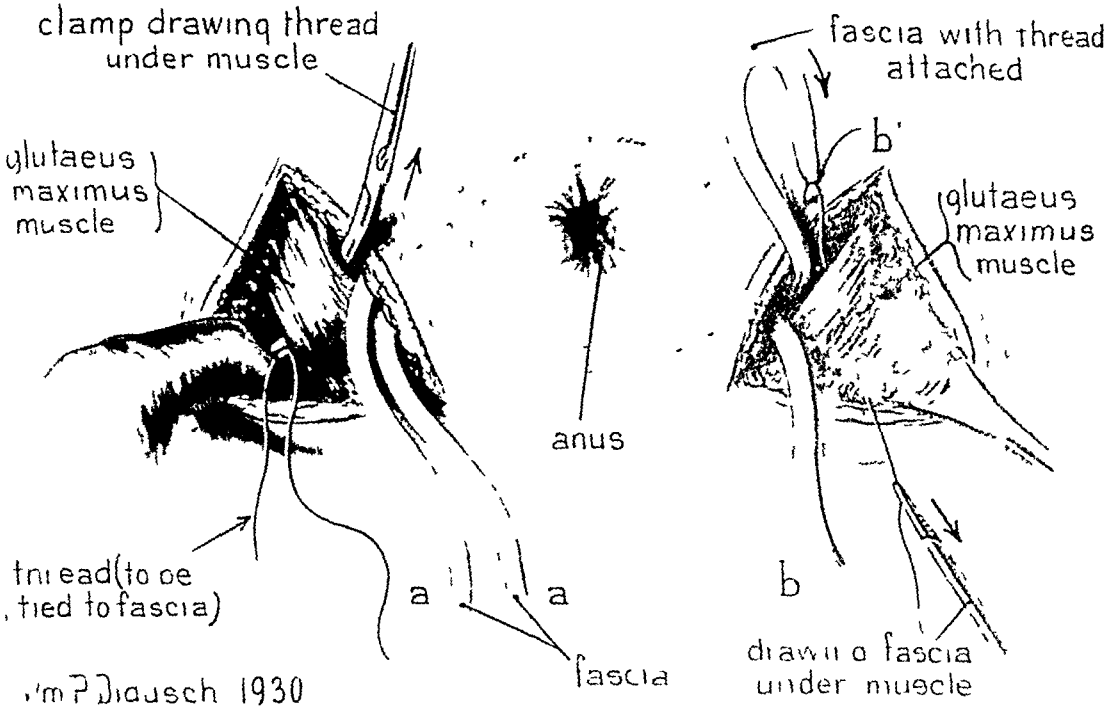


FIG 2—The outer ends of the strips of fascia are passed around the bundles of the glutaeus muscle (Arch Surg, 24, 124, 1932)

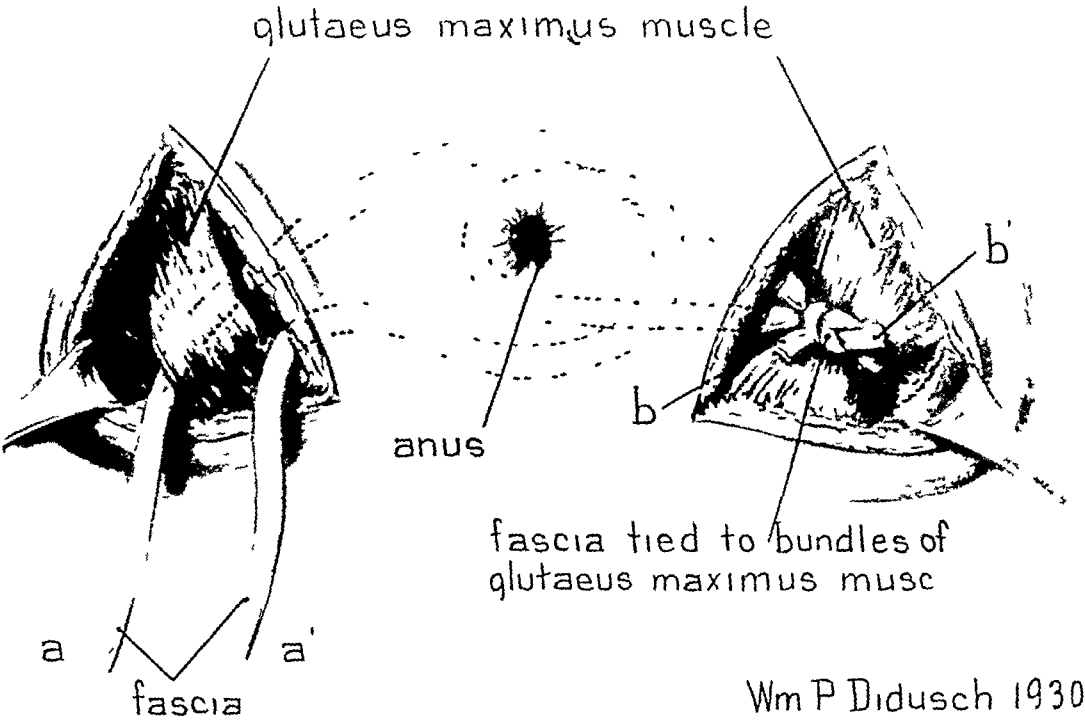


FIG 3—The loops of fascia are tied on the right side ready for tying on the left (Arch Surg, 24, 124, 1932)

relief. A number of them were almost completely incapacitated by reason of their inability to control the anal outlet. Several had had previous unsuccessful surgical attempts directed at restoring function.

The patients ranged in age from 12 to 72 years. Twenty-one, or 70 per cent, were female, while nine or only 30 per cent were male. There were no deaths in the group.

TABLE I

CONDITIONS WHICH DIRECTLY OR INDIRECTLY HAVE CAUSED ANAL INCONTINENCE

Condition	Number of Cases
Operation for anal fistula	12
Congenital abnormality	5
Operation for hemorrhoids	4
Rectal cancer (following excision of)	2
Perineal laceration	2
Prolapse of rectum	2
Megarectum (following excision of)	1
Trauma	1
Anal ulcer	1
Total	30

In Table I are presented the conditions which directly or indirectly have caused anal incontinence among this group. As would be expected this complication has occurred most frequently in connection with anal fistula. In Table II are listed the results of the fascia plastic operations. Eighty-seven per cent demonstrated some improvement and in 40 per cent the results approximated normal control.

TABLE II

RESULTS IN 30 CASES OF FASCIA PLASTIC OPERATION FOR ANAL INCONTINENCE

Result	Number of Cases	Per Cent
Excellent	12	40.0
Good	9	30.0
Fair	5	16.6
Unsatisfactory	4	13.3
Total	30	

In appraising this operation, it must be remembered that certain conditions are necessary before it can have a reasonable chance of success. The gluteal muscles must be properly innervated and able to contract voluntarily. The individual must possess the intelligence to use the muscles to contract the anal canal, and the patience to practice this contraction frequently, for the measure of control given by the operation is voluntary and not automatic, as is the normal sphincter mechanism. As in all plastic operations, infection may spoil the result, and because of the proximity of the anus, infection not infrequently occurs. In six of these cases, fragments of the fascia were discharged from the wounds, but in only two of these six was the result unsatisfactory. Hence, infection and even loss of fascia may occur without necessarily jeopardizing the result. In general, the procedure has proved its value. In spite of some failures, the majority of cases have been benefited, and in certain

instances brilliant results have been obtained. It should be noted, in conclusion, that a failure does not make the patient any wiser, and does not prevent a repetition of attempts by the same or other methods.

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- ¹ Stone, H. B. Plastic Operation for Anal Incontinence. *Arch Surg*, 18, 845, March, 1929.
- ² Wreden, R. R. Method of Reconstructing Voluntary Sphincter. *Am Arch Surg*, 16, 841, March, 1929.
- ³ Stone, H. B. Plastic Operation to Restore Voluntary Anal Control. *JAMA*, 97, 1205, October 24, 1931.
- ⁴ Stone, H. B. Plastic Operation for Anal Incontinence. *Arch Surg*, 24, 120, January, 1932.

DISCUSSION—**DR HARRY J. WARTHEN, JR.** (Richmond, Va.) I would like to add another successful case to the series Doctor Stone just reported. Several years ago I reported the case of a child six or seven years of age, born with an imperforate anus. An immediate perineal opening was made but apparently no repair to the sphincter had been attempted. In addition, the child had a megacolon. The patient was operated upon in stages, the megacolon was corrected by a lumbar sympathectomy, and Doctor Stone's fascia strips were employed to repair the anus. I saw the child for six months following operation, and each time the parents stated the control was improving. The last time they said he had complete control and no longer soiled himself. This was in spite of the fact that some infection occurred, and the child was of somewhat inferior mentality. I believe this patient was younger than any in Doctor Stone's group.

DR DERYL HART (Durham, N. C.) I would like to report a case in which fascia was employed to replace a congenital defect in the sphincter muscle in a six- or seven-year-old girl. The sphincter muscle did not pass anterior to the rectum but ended on each side of the perineal body, where a dimple was produced by the sphincter muscle when a stimulus was applied to the perineum.

A small incision was made just posterior to the dimple on each side, and well away from the anal orifice. The sphincter muscle was located and dissected free on each side for a distance of 0.5 to 1 cm. without disturbing its point of fixation. By blunt dissection, a tunnel was made between the rectum and vagina, and connecting the two incisions. A loop of fascia was passed around the muscle on each side, pulled snug, and sutured with silk. Care was taken to avoid sufficient tension to interfere with the blood supply of the sphincter muscle. The incisions were closed, and primary healing was obtained. The child, who had had fecal incontinence since birth, had good control from the day of operation without the necessity of any educational program.

This paper was read before the Fifty-third Annual Session of the Southern Surgical Association, Hot Springs, Va., December 10, 11, 12, 1940.

ARRHENOBLASTOMA OF THE OVARY

FRED KROCK, M D, AND S J WOLFERMAN, M D

FORT SMITH, ARK

IT is only within comparatively recent years that clinicians have begun to entertain, seriously, the thought that certain neoplasms may be able to function to a certain extent similar to the tissues from which they arise, although examples of such function have been before us for many years. For instance, Hansemann, in 1900, observed and described the production of bile in the brain by a metastatic nodule from a primary carcinoma of the liver. In 1930, Tuiley somewhat clarified the situation by pointing out the similarities between neoplastic and normal cells both from the standpoint of histology and physiology. Many striking instances can be called to mind, such as hyperinsulinism due to adenomata of the islands of Langerhans, and hyperthyroidism with struma ovarii.

In 1930, Robert Meyer reported, under the term "arrhenoblastoma," a series of ovarian tumors showing, microscopically, what has been interpreted as testicular elements, and many of which possessed the bizarre property of masculinizing their hosts. As the borders of the field of endocrinology advanced, it was soon shown that this striking alteration of secondary sexual characteristics was not limited to ovarian tumors. Cushing, for instance, has reported a number of instances apparently associated with basophilic adenomata of the pituitary, and Walters found a similar picture with certain tumors arising from the cortex of the adrenal glands. As the number of reported cases increased in which the metamorphosis of the individual was associated with ovarian tumors, it became evident that even the histologic structure of the tumor was by no means uniform. In fact, a paradox appears in which the most highly differentiated tumors, namely, those in which the testicular structure is unmistakable, show the least degree of masculinization, while in the undifferentiated types, in which connective tissue elements predominate, virilism is always marked.

In 1932, we published a case report of an additional instance of an arrhenoblastoma of the ovary, classified by Meyer as belonging to the atypical group, with marked changes in the secondary sexual characteristics, and almost complete reversion to normal following extirpation of the tumor. The study of the recurrence which occurred in this particular case gives additional evidence on what may be the exact nature of some of these unusual tumors, and the report of which has been made the basis of this paper.

Case Report—An 18-year-old schoolgirl, with amenorrhea, virilism, and hirsutism of four years' duration, was operated upon, April 14, 1932, for the removal of a large tumor of the left ovary, having the microscopic characteristics of the atypical group of arrhenoblastomata suggested by Meyer. There was a marked and prompt restoration

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to normal femininity, including resumption of a normal menstrual cycle within six weeks following operation

One year later, the patient was apparently in good health and said that she had never felt better in her life, although a slight coarsening of the voice and increase in beard over the face was noted over what had existed at examination several months previously

FIG 1

FIG 2

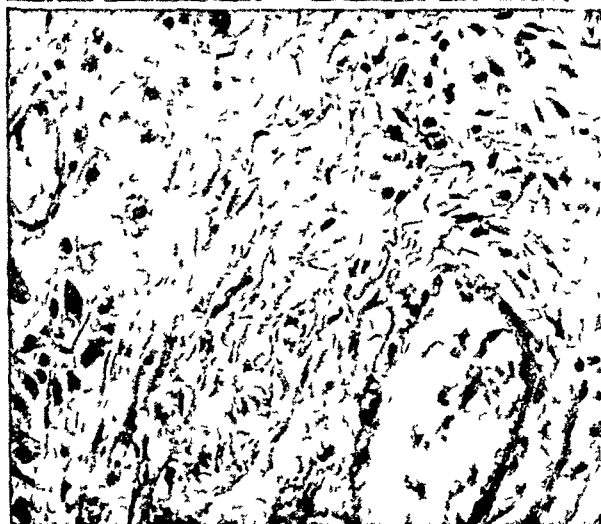
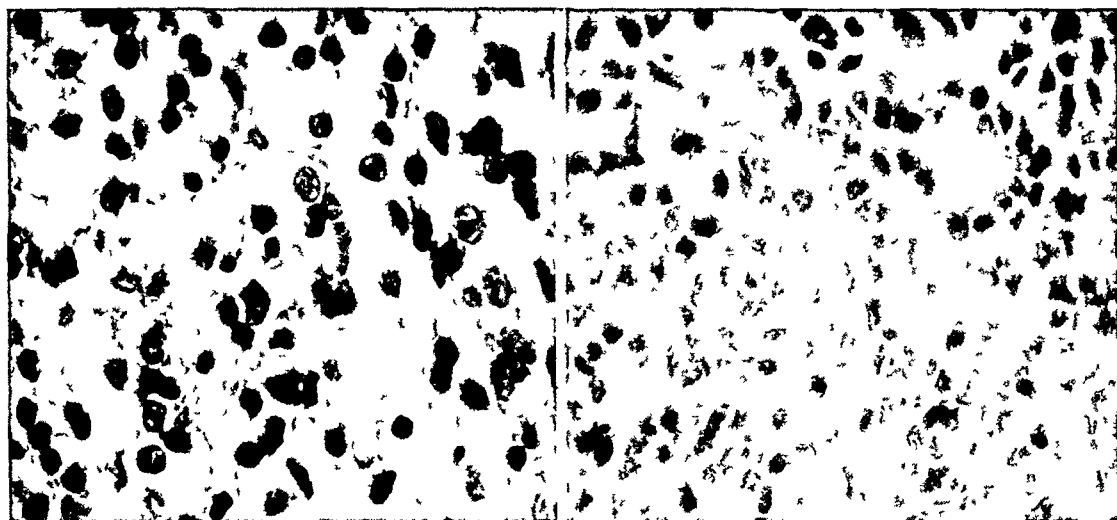


FIG 3

FIG 4

FIG 1—High power view of block from original tumor. Note loose, indeterminate structure

FIG 2—High power field from original tumor. Note tendency to tubular formation

FIG 3—Low power field from another block in original tumor. The pleomorphic character of the tumor cells is here evident and in itself suggestive of a teratoma

FIG 4—Photograph of resected omentum showing the two tumor nodules of the first recurrence

On June 1, 1933 (13 months later), while drying dishes, she turned suddenly, and was stricken with an abdominal pain of such severity that she had to be helped to a chair, where she collapsed. On admission to St Edward's Mercy Hospital she complained of severe lower abdominal pain, and had vomited several times. On examination the patient presented an anxious facies, and appeared to be in shock. Temperature 96° F, pulse 140, weak and variable, blood pressure 90/60. There was marked tenderness in both lower quadrants but no rigidity. A blood count showed 17,000 leukocytes, with a Schilling left shift of 38. A diagnosis of acute abdominal catastrophe was evident, and exploration under ether anesthesia was carried out through the old low midline scar

Approximately one liter of free and clotted blood was encountered upon entering the peritoneal cavity. Two tumor nodules were found attached to the omentum. The first of these was 50x30x10 mm, it was soft, lobulated, reddish-orange, and resembled an immature chicken egg. The second nodule measured 35x25x15 mm, and was white, harder, and had been split in two the fissure crossing a large omental vein which was the source of the hemorrhage. The nodules were removed with a large margin of the omentum. Further exploration showed the left ovarian region to be clear. The right ovary was 3x2.5x2.5 cm, and contained graafian follicles and corpora lutea of varying sizes and stages of development. The uterus was of normal vaginal size, shape, and consistency. No other tumor nodules could be found.

On section, the first tumor was of a uniform consistency, cutting like a moderately firm lipoma. Microscopic sections of this tumor showed a loose cellular structure, with areas of rather typical embryonic cartilage (Fig 7). A well-defined capsule surrounded the periphery.

The second nodule was harder, whitish on section, and showed several areas of hemorrhage. The microscopic structure was that of a spindle-cell sarcoma (Fig 6) and closely resembled similar areas in the original tumor. The nuclei were large and mitotic figures testified to a rather rapidly growing process.

Convalescence was uneventful, and the patient remained in good health until August 24, 1933 (three months later) at which time she entered St. Joseph's Hospital at Booneville, Mo., complaining of abdominal pain of six days' duration and diarrhea. The following portion of the case report is from the records of Drs. Alex and C. H. Van Ravenswaay, who were kind enough to give us the follow-up.

"At this time a heavy growth of hair on face, legs and axillae was noted, with a masculine type of crines (pubic hair distribution). Chest examination, including fluoroscopy, was negative. There was a perceptible bulging in the lower quadrant, where a hard, slightly movable mass the size of a head could be easily outlined. Temperature 100° F, pulse 140, respirations 48, blood pressure 132/74. Blood examination showed 3,820,000 erythrocytes, 60 per cent hemoglobin, 17,600 leukocytes, and a differential of 90 per cent polymorphonuclear neutrophils, 6 per cent stab cells, 2 per cent myelocytes, and 2 per cent small lymphocytes. The Kahn test was negative and blood Group II. Urinalysis showed one plus albumen and three plus hyaline casts. On August 26, 1933, exploratory celiotomy disclosed a large, soft multilocular tumor, built up of mucofibrous tissue, very friable, and adherent to the abdominal wall. It bled on the slightest manipulation. It had apparently arisen from the right ovary. Seven thousand cubic centimeters of bloody fluid were aspirated from the peritoneal cavity. Because of the danger of uncontrollable hemorrhage, and inability to completely extirpate the tumor, the abdomen was closed. Several fragments of tumor were removed for microscopic study. Blood transfusion was given postoperatively. Deep roentgenotherapy to the abdomen was started. The abdominal fluid recurred, and on September 5, 1933, 2,000 cc were aspirated. The patient gradually grew weaker and expired, September 16, 1933. Permission for necropsy was not obtained."

The slides of tissue from this recurrence were kindly loaned to us by the Doctors Van Ravenswaay for study. Part of the section consists of closely packed round nuclei with practically no intercellular substance, and resembling, grossly, a smear from tissue rather than cut sections (Fig 8). The nuclei, for the most part, are round and hyperchromatic, and variable as to size. The majority are macrocytic. In a few areas, the nuclei are arranged in the form of rudimentary tubules (Fig 9), resembling the structure seen in the original tumor. Differentiation, on the whole, is very poor. The tissue is abundantly supplied with poorly constructed capillaries distended with erythrocytes. No whorls or spindle cells are noted in these areas.

Adjacent areas show a mucoid type of connective tissue, reminiscent of Wharton's jelly in the umbilical cord. Definite wavy fibrils are interspersed between the spare nuclei. Both spindle-shaped and large, round nuclei are evident, with the latter pre-

dominating Mitotic figures and atypical cell divisions are abundant The cells themselves are circular with interlacing fibrils

Probably no chapter in oncology offers more exciting possibilities for speculation than does this interesting group of masculinizing ovarian tumors In the first place no present-day classification of ovarian tumors is entirely satisfactory from the standpoint of morphogenesis Explanation of the origin of comparatively simple forms, such as pseudomucinous cystadenomata and papillary types, leaves much to be desired It is little wonder, then, that in dealing with complex neoplasms, such as the various forms of the so-called arrhenoblastomata, we fully unleash our imaginations in the attempt to correlate physiologic manifestations with morphology as a key to the solution A number of theories have been advanced, the most prominent of which are

(1) *Hermaphroditic Basis*—Pick first suggested that these tumors might be associated with hermaphroditism or pseudohermaphroditism As the number of reported cases increased, it soon became apparent that this view was not tenable, because, as a rule, the individual has developed anatomically and physiologically along perfectly normal female lines until the tumor began to manifest its presence by a transformation of secondary sexual characteristics In other words bisexuality was not present from birth, as must obtain with true hermaphroditism

(2) *Gonadal Protective Effect*—Halban has insisted that the zygote is primarily male, female, or hermaphroditic from the moment of fertilization, and that the gonads exert only a protective effect and not a formative influence upon the development of secondary sexual characteristics In other words, all the primary and secondary sexual characteristics of the individual are established from the beginning For the full development of the secondary sexual characteristics, a protective effect from the gonads themselves is necessary The tendency of certain tumors to change the secondary sexual characteristics can then be explained by assuming that the tumor is able to exert an hyperprotective effect upon latent male elements present When the tumor is extirpated, reversion occurs because of the withdrawal of the male protective influence, and further suppression by resumption of normal ovarian function

(3) *Origin of the Tumor from Latent Male Elements*—Robert Meyer, under the term "arrhenoblastoma," groups together a rather heterogeneous collection of ovarian tumors varying from apparently typical testicular adenomata, without endocrine effects, to spindle-cell sarcomata, with an occasional rudimentary tubule and associated with extreme masculinization He suggests the explanation that the cell mass destined to become the sex gland is at first indistinguishable as male or female, and that, eventually, cords of cells appear beneath the germinal epithelium, and extend down toward what later becomes the hilum In the male, these structures become permanent as seminiferous tubules, while in the female, atrophy takes place and they remain as abortive seminiferous tubules or medullary cords The true ovarian struc-

ture is then built up around them and, as Novak expresses it, "they become fossilized in the rete ovarii." Meyer feels that these cell remnants retain their male potentialities, and may give rise to tumors with masculinizing tendencies. The stumbling block here is that no one has an adequate ex-



FIG 5—Drawing of tumor nodule of first recurrence with tear into omental vein and subsequent hemorrhage

planation of just what factor enters into the picture to cause these presumably normal cells to spring into such vigorous activity as to overcome all previously fully developed ovarian tissue.

(4) *Teratomatous Origin*—Popoff, in 1930, in reporting a case of testicular adenoma of the ovary suggests that these tumors may represent one-sided teratomata, citing Ewing's similar conclusion as to the origin of embryonal carcinomata of the testicle, and L'Esperance's concerning embryonal carcinomata of the ovary. Buttner, in a report of 25 cases collected in 1932, raises the question whether an arrhenoblastoma may not be, after all, only a teratoma of the ovary in which the other tissue elements, usually found in teratomata, are lacking due to their destruction by sarcomatous degeneration. Pick has definitely stated that a single element in a teratoma may predominate and obscure, or even suppress, all other tissue elements. Attention was called by us, in 1933, to the possible teratomatous origin of these tumors, after finding of cartilage in the first recurrence in our case. McLester and Ledbetter, in 1936, reported further definite confirmatory evidence of this view, in their case.

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TABLE I
TABULATION OF REPORTED CASES
Modified from Baldwin-Gafford

Author	Age	Involved Side	Pathologic Anatomy
1 Pick	34	Right	Typical testicular adenoma right ovary
2 Schrickele	26	Left	Typical tubular adenoma
3 Neumann	32		Typical tubular adenoma Interstitial cells
4 Berner	22		Typical tubular adenoma
5 Blair Bell	19	Right	Part tubular, part solid Interstitial cells
6 Meyer	46	Left	Carcinomatous tubular adenoma
7 Meyer	47	Right	Carcinomatous tubular adenoma
8 Neumann	56	Both	Carcinomatous tubular adenoma
9 Meyer (Priebatsch)	44		Carcinomatous tubular adenoma
10 Meyer (Phelan)	20	Left	Typical testicular adenoma
11 Miller	30	Left	Typical testicular adenoma No masculinizing
12 Popoff	31	Right	Tubular adenoma with solid portions
13 Meyer (Cupei)	16	Left	Part typical, part atypical, and part solid carcinomatous
14 Meyer (Univ Clin)	23	Right	Major portion atypical
15 Meyer (Bauer)	66	Left	Part tubules
16 Meyer (Mackenrodt)	35	Right	Cords and portions similar to granulosa cells
17 Meyer	31		Solid epithelial cords Narrow openings
18 Meyer	36		Tubules Dense epithelial infiltration
19 Spielman	26	Right	Tubules and cords
20 Novak-Long	20	Left	Definite tubules Also typical sarcoma
21 Szathmary	25	Right	Marked polymorphism Large solid areas and areas of epithelial tubules
22 Moots		Left	Tubules Fibroblastic sarcoma
23 Meyer (Orru)	40	Left	Pseudomucinous tumor
24 Meyer (Knebel)	28	Left	Mucous membrane in tumor
25 Meyer (Specht)	26	Left	Granulosa cells in tumor
26 Halban	31		Small-celled carcinoma, solid with tubular shapes
27 Wagner	25	Left	Epithelial solid tumor Tubules
28 Kleinhans	31	Left	Rests of epithelial new growths Regressive changes
29 Krause	41	Recurrence R	Epithelial cord-like arrangement
30 Geisler		Right	Cord-like carcinomatous tumor Mucous epithelial rests
31 Strassmann	24	Right	Atypical adenoma, part carcinoma, part sarcoma, mucous cysts
32 Sedlis	16	Left	Epithelial strings, partial tubular, cystic degeneration
33 Taylor-Wolferman-Krock	18	Left	Irregular medullary cords Rudimentary tubules
34 Eerland	35	Recurrence R Right	Cartilage in recurrence
35 Baldwin-Gafford	24	Left	Solid periphery with cystic areas within, tubules and cords
36 Sellheim	47		Most of tissue sarcoma, primitive tubules and cords
37 Bingle Schultze	47		Bone formation
38 Mathias-Tschirdewann (Sedlaczak)	19		Solid epithelial tumor
39 Buettner	66	Left	Strings and fields of epithelial cells
40 McLester	32	Right	Solid tumor Tissue resembling thyroid
41 Benecke	28	Left	Solid epithelial tumor Strand-like villous and tubular portions
42 Benecke	26	Left	Cyst containing mucous producing cells, fat, cyst with ciliated columnar epithelium, gland-like epithelial cells
43 Norris	34	Right	Tubules, mucous cysts, sarcomatous portion
44 Hitzanides	19	Right	Cavernous network of cells
45 Foderl	17	Left	Cords of epithelial cells
46 Depuy	61		Sarcoma Cubical carcinomatous cells
47 Anderson		Right	Tumor suggesting fibroma Proved to be epithelial
48 Haffner	32	Right	Atypical arrhenoblastoma
			Alveoli, tubules hypernephroma-like cells Interstitial cells
			Cystic Pseudomucinous substance Interstitial cells 18 mouse units of folliculin in 24 hr urine

Author	Age	Involved Side	Pathologic Anatomy
49 Glaser Erhard Hempel	27	Left	Spindle cells Mucous elements (fibroma with mucoid degeneration) Calcium deposits
50 Kleistman	30	Left	Large cells with nuclei Protoplasm contains drops of fat
51 Pires	22	Left	Papilliferous cystadenoma with sarcomatous degeneration Tubules, cords Lutein like cells Supra renal cortex
52 Xavier Junqueira	31	Right	Tubules, cords Granulosa cells Histologic picture pleomorphic
53 Kleine H O	54	Right	Tubules, spindle form cells Interstitial cells
54 Kleine H O (P Wolff)	49	Right	Tubules Interstitial cells
55 Kleine H O	55	Both	(Teratoma in left ovary) skin hair fat bones Right showed tubules interstitial cells sarcoma
56 Kleine H O (Bachel)	52	Right	Tubules solid cords interstitial cells
57 Schiller	17	Left	Interstitial cells epithelial cords
58 Dockerty MacCarty	25	Left	Alveolar cells interstitial cells
59 Dockerty-MacCarty	31	Left	Testicular tubular adenoma Absence of interstitial cells Marked virilism
60 Dockerty MacCarty	15	Right	Cords, tubules interstitial cells
61 Dockerty MacCarty	51	Right	Tubules, cords, no interstitial cells No clinical virilism Recrudescence of bleeding
62 Neumann		Left	Tubular testicular adenoma
63 Cabot case No 25351	29	Right	Well formed tubules Adenoma tubulare testicular Interstitial cells
64 Boltuch	28	Left	Connective tissue tumor Cysts with cuboidal epithelial lining Interstitial cells No tubules Epithelioid cells
65 Luzuy	16	Right	Fibromyoma cuboidal epithelial cells No tubules Interstitial cells
66 Aburel Marzi Dobrovici	22		No true tumor Two nodules, glandular tubules Interstitial cells No virilism
67 Sarkar Tribedi	15	Left	Tubules sarcoma Different sections showed different types of cellular pattern
68 Wijssenbeek Plate	28	Left	Multicameral cyst Tubules Fat containing cells resembling interstitial cells
69 Hardjosoekatmo	23	Left	Mucous cysts Epithelioid cells Tubules
		Right recurrence Death from recurrence	
70 Xavier-Junqueira	43	Right	Sarcomatous degeneration Epithelial cysts Deep yellow pigment Tubules Interstitial like cells

With this theory in mind we have studied all the available reports on cases listed as anthenoblastomata in the literature, and have been able to collect 70 cases (Table I). A study of this material would seem to point toward several significant facts. In the first place, the conclusions of investigators on sex reversal, that the right ovary exhibits testicular transformation more often than the left in animals, is not borne out in the human, since the tumor was found on the left side in 31 cases as against 26 cases on the right. The affected side is not mentioned in 11 cases and in two it was stated as occurring on both sides. It is also to be noted that the histologic pictures, as reported, lack the necessary degree of uniformity to be convincing that this unusual tumor is a distinct pathologic entity. And, lastly, we have been able to find 24 instances in this group of cases in which suggestions of dermal tissue elements were found on routine examination (Table II).

Since Ewing has reported finding only a single island of cartilage and a single epidermoid nest in a large embryonal carcinoma of the testis or teratoma in serial section, it would seem only reasonable that this method of

study applied to these tumors would yield an even greater percentage of interstitial tissue elements than was found in routine sections. In our own case, a section from each of 50 blocks from different portions of the tumor was studied, but this is still an infinitesimally small number in a tumor weighing 990 Gm.

FIG. 6

FIG. 7

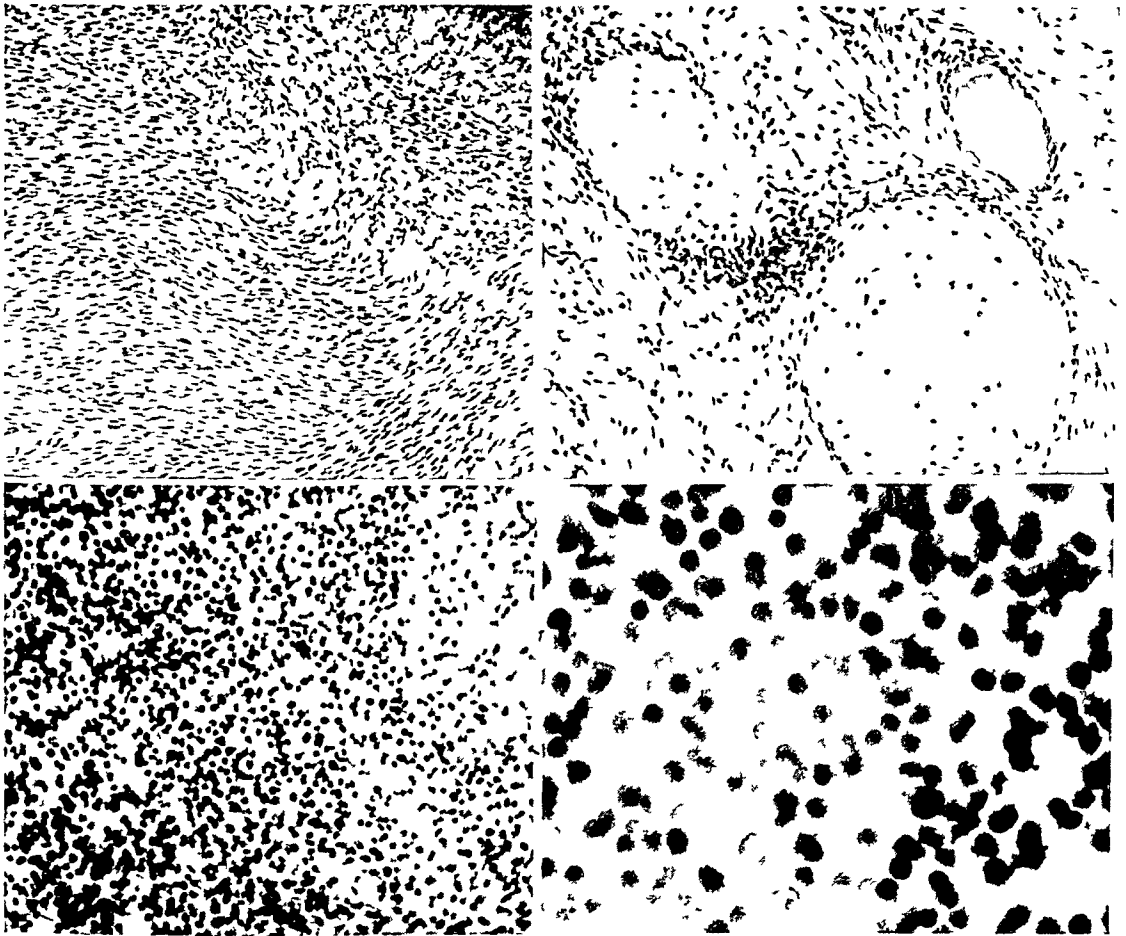


FIG. 8

FIG. 9

FIG. 6—Low power field from one of the nodules removed during the first recurrence. The same spindle cell sarcomatous structure appears here as was found in the original tumor.

FIG. 7—High power field from the second nodule removed during the first recurrence. Typical cartilaginous islands are apparent.

FIG. 8—Low power field from second recurrence. Note anaplastic type of growth.

FIG. 9—High power field from second recurrence. Note tubule formation, and similarity of structure of original tumor as shown in Figure 2.

In a number of the reported cases, the presence of interstitial cells is noted, the identification of these cells being based upon morphology as well as their affinity for fat stains such as Sudan III. Popoff in his case of testicular tubular adenoma of the ovary showed, definitely, that these large clear, fat laden cells were epithelial cells which had undergone lipoid degeneration, rather than being true interstitial cells which are considered to arise from mesodermic elements.

Alteration of secondary characteristics in the female is not limited to one particular group of ovarian tumors. We find, in the literature, many reports of masculinizing ovarian tumors in which histologic examination has failed to

disclose the presence of testicular elements, even by men familiar with Meyer's work Studdiford, for instance, reports a case of granulosa cell carcinoma which produced clinical masculinization, and cites Bergstrand, of Sweden, as

TABLE II
TRIDERMAL TISSUE ELEMENTS FOUND IN 70 CASES

Tissue Elements	No of Cases
Mucous membrane	9
Granulosa cells	3
Cartilage	1
Bone	1
Thyroid	1
Ciliated epithelium	1
Pseudomucinous tissue	2
Lutein cells	1
True teratoma	1
Sarcoma	2
Suprarenal cortex	1
Fat	1
Total	24 or 34%

having seen several similar cases, and who subsequently studied some of Meyer's material and reclassified it as granulosa cell carcinoma Maxwell's case proved to be aberrant cortical tissue in the ovary A case reported in the Massachusetts General Hospital clinicopathologic conferences with a typical picture of acquired virilism, with regression to normal after operation, was found by Malloy to be an embryonal carcinoma of the ovary Lutein cell tumors, dermoids and true teratomata, with clinical virilism, have been reported by Schiller, Cosaresco and others Goldberg records a case of true sarcoma of the ovary with masculinization

In other words, we have, on the one hand, the so-called "arrhenoblastoma" with a variable picture of masculinization clinically but with what apparently are testicular elements histologically, and, on the other hand, a number of different types of ovarian neoplasms in which the predominant tissue is other than testicular, but with clinical virilism The one thing common to two such widely divergent pictures is the presence of tridermal tissue elements, which can be demonstrated by routine studies in approximately one-third of the cases To create a new pathologic entity, based upon the predominant tissue present, as has been done with arrhenoblastomata, would lead to hopeless confusion In the final analysis, our present knowledge is still deficient concerning the exact origin of all the factors controlling the development of secondary sexual characteristics Upon this basis, it is our plea that all masculinizing ovarian tumors be classified as teratomata with a one-sided development, be such development testicular elements (either in the form of interstitial cells or seminiferous tubules), adrenal cortical remnants, or even other tissues or their anlagen whose rôles at present under normal conditions, in the development of the secondary sexual characteristics of the individual, are not fully understood Or we may retain the term "arrhenoblastoma" to indicate such a "clinicopathologic" condition as suggested by Norris, rather than regard it as representing one constant pathologic entity to be pigeon-holed thus by any pathologist inspecting the tissue microscopically

CONCLUSIONS

(1) The final follow-up on a previously reported case of arrhenoblastoma of the ovary is presented

(2) Evidence is brought forth to support the conclusion that, from a purely pathologic standpoint, arrhenoblastomata may represent one-sided teratomata

The authors wish to express their appreciation to Dr J L Goforth for the excellent photomicrographs presented, and to the Doctors Van Ravenswaay for allowing us to report the final follow-up from their case records, and for the loan of slides showing the terminal stages of the tumor

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DISCUSSION—DR EMIL NOVAK (Baltimore Md) The first case of arrhenoblastoma reported in this country under that designation was the one whose later history has just been described by Doctor Krock. Similar tumors had been previously described but under incorrect diagnoses, as the pathologic entity now designated as arrhenoblastoma was then not known. We now have in our laboratory specimens or slides of 11 of these rare tumors, though most of these have been sent in for diagnosis from outside sources.

Doctor Krock has laid especial stress upon the finding of teratomatous elements in a number of the reported cases and suggests, as others have done, that arrhenoblastoma is to be looked upon as of teratomatous origin. I do not think that the evidence can be considered convincing. Dysgerminoma, in my experience, is more apt to be associated with teratomatous elements than is arrhenoblastoma, but this does not justify the conclusion that it is in itself a type of teratoma.

No one, of course, can speak with assurance as to the etiology of arrhenoblastoma and I, for one, do not feel convinced of the entire adequacy of the generally accepted theory of Robert Meyer, who has done so much to clarify this subject for us. We know too little as yet, of the factors concerned in sex differentiation. It has always seemed significant to me that the anlage of the adrenal cortex in the early embryonic phase is directly continuous with, and indistinguishable from, that of the ovarian medulla. This may explain why certain tumors of the adrenal cortex and such ovarian medullary tumors as arrhenoblastoma produce identical clinical pictures, especially as regards masculinization phenomena.

There is no stereotyped histologic picture in arrhenoblastoma and the term really refers to an histologic family rather than to any one histologic type. To interpret and diagnose these tumors one must have some idea of the early embryology of the ovary.

From a clinical standpoint, the early symptoms of arrhenoblastoma, such as amenorrhea and flattening of the breasts are not to be looked upon as masculinizing, but rather as merely defeminizing, that is, subtracting something from the feminine characteristics of the patient. Later come the more positive evidences of masculinization, such as hirsutism, deepening of the voice, and hypertrophy of the clitoris. Hirsutism, in itself, is certainly not always a sign of masculinization, for it is often found in women who otherwise are typically feminine, and who menstruate normally and bear numerous children. It may however, form a part of the masculinization syndrome, when combined with other such symptoms as I have mentioned.

I make this distinction because the mistake is often made of suspecting arrhenoblastoma when an ovarian tumor is found in a woman who also exhibits the picture of the so-called virilism. The latter, however, will usually be found to have been present since puberty and it will not disappear after removal of the tumor, which will be found not to be an arrhenoblastoma. When, on the other hand, a previously normal woman develops masculinization phenomena, and an ovarian tumor can be palpated the suspicion of arrhenoblastoma is fully justified, though, even then, mistakes will occur. An exactly similar picture can be produced by certain rare adrenal tumors of the ovary, while in some cases a tumor of the adrenal cortex, combined coincidentally with a simple cystadenoma of the ovary, may simulate, perfectly, the characteristic syndrome of arrhenoblastoma.

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CARCINOMA OF THE FUNDUS OF THE UTERUS

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THERE ARE varied opinions concerning the best treatment for the patient with carcinoma of the body of the uterus. Masson and Gregg¹¹ feel that the standard treatment of carcinoma of the body of the uterus is a total hysterectomy with bilateral salpingo-oophorectomy. Richardson¹⁵ stated, in 1935, that the complete surgical extirpation of the uterus together with both tubes and ovaries still remained the best therapeutic attack on cancer of the corpus uteri. Sackett,¹⁶ in 1937, preferred combined therapy whenever it was possible. In 1937, Scheffey and Thudium¹⁹ advocated preliminary irradiation with a panhysterectomy in selected cases. Martin¹⁰ takes the position, that if a curettage after irradiation showed malignant tissue, then an operation was advised for certain groups. Kilgore⁸ stated that, in 1936, the California Cancer Commission recommended an hysterectomy with preoperative irradiation in cancer limited to the uterus, and irradiation therapy in cancer extending beyond the walls of the uterus. Because of these varied opinions, the writer has made a study of a group of our own cases, with particular endeavor to evaluate the end-results of treatment.

There were 110 case records of patients with this pathologic entity, who had been seen in the Scott and White Clinic during the 20-year period, from 1921 through 1940. Eighteen patients of this number were excluded from this study. Six of the 18 had been treated elsewhere, and came to the clinic for observation only. Four others declined treatment, and eight were found to have diffuse metastasis and were regarded as hopeless, so no treatment was advised. The remaining 92 patients, of the 110, entered the hospital for treatment, and they form the basis for this detailed review. The diagnosis of carcinoma of the uterine fundus was proved histologically in every case. Follow-up data to date have been obtained on all patients. All patients with both cancer of the uterus and of the ovary were omitted from this study except two. In these, there was little question but that the cancer was primarily of the uterus. Cancers of the fundus and cervix were excluded also, unless the lesion was rather definitely primary in the corpus.

The incidence of carcinoma of the fundus is decidedly less than is that of the cervix. Sackett¹⁷ reported the ratio of body carcinoma to that of the cervix, as one to five, Cile and Elias,⁴ one to three, Scheffey and Thudium,¹⁹ one to nine and five-tenths. The incidence in our clinic has been approximately one to six. During this same period of time, 17 patients have been seen with sarcoma of the uterus. In our clinic, there have been seen six

cancers of the cervix to one of the fundus, and six carcinomata of the fundus to one sarcoma

The etiology of fundal cancer remains obscure Taylor,²¹ after an extensive study of the problem, wrote that the relationship of hyperplasia to carcinoma of the endometrium has an etiologic and clinical aspect He reported

TABLE I
THE AGE INCIDENCE

Age	No of patients	Age	No of patients
30 to 40	3	60 to 70	19
40 to 50	16	70 to 80	5
50 to 60	49		

The average age was 55
19 or 20.6 % were under 50
73 or 79.4 % were over 50

the association of endometrial hyperplasia and carcinoma in the same uterus McMuney⁹ concludes that a functional abnormality is present in the reproductive organs of women with this condition Counseller³ suggested that this type of cancer is in one manner related to the ovarian hormones Heriell⁷ wrote "It seems reasonable to conclude that the unopposed action of estrin with its resulting effect on the endometrium is the basic principle at work in the development of malignancy of the endometrium of those individuals who possess the genetic factor necessary for the development of cancer "

It is the consensus of opinion that parity is not an etiologic factor In this case review, it was found that 87 were married and five were single Seventy-three per cent of the married women were mothers Fibroid tumors are considered to have but little if any etiologic significance in this disease, however, the development of cancer from endometrial polyps does occur Thirteen patients of this series were found to have uterine polyps

Crossen and Hobbs⁵ found that cancer of the uterine fundus tended to occur, definitely, more often in the woman who had a late menopause Therefore, the patient with a history of a late menopause should cause us to suspect some type of endometrial lesion In our study, it was found that 65 patients, or 70.6 per cent, developed symptoms after the menopause and 27, before the menopause The average time of the menopause, in those patients who had cancer beginning after the climacteric, was 49 years

Patients with cancer of the uterine body are definitely older on the average than are those who have a malignancy of the cervix A majority of statistics shows that the average age incidence is in the late fifties Healy and Brown⁶ gave the average age incidence as 55 Counseller wrote that 90 per cent of these patients were over 45 Our statistics showed that 19 patients were under 50, and 73 were over 50 years of age The average age was 55 years, 79.3 per cent being past 50 (Table I)

The cardinal signs and symptoms are a metroirrhagia, a menoirrhagia, a vaginal discharge, and pain We would stress the significance of abnormal vaginal bleeding, which is the predominant sign of this condition According to Norris and Dunne,¹³ it is the first sign in 80.5 per cent of the cases Pratt¹⁴

found, in a study of 71 cases, that there was microscopic to gross bleeding in all of the 71 cases. We found that 24 of the 27 patients, who developed cancer before the menopause, gave histories of prolonged or irregular bleeding. Sixty-two of the 65 patients, who had symptoms after the menopause, gave bleeding or a blood-tinged discharge as their most significant symptom. Abnormal vaginal bleeding was the symptom of first importance manifested by 93.5 per cent of the entire group. The fact should be emphasized that the postmenopausal bleeding is usually small in amount, and sometimes it is just a spotting. It may occur at intervals of a few or several weeks, or even several months. Profuse bleeding, which happens with so many benign conditions of the uterus, is seldom seen in carcinoma of the fundus, except occasionally in advanced cases. Because of the small amount of bleeding at infrequent intervals, seen in many cases, it is difficult for the patient to appreciate its significance. Patients quite frequently regard the change in amount and character of flow as a natural accompaniment of the menopause and, therefore, defer consulting a physician. It is hard to evaluate the significance of a vaginal discharge for there are so many pathologic conditions which produce discharges. However, a number of patients with uterine malignancies do give histories of a brownish, watery discharge, sometimes irritating in nature.

Pain is a symptom in approximately one-third of the patients with carcinoma of the fundus of the uterus. Healy and Brown reported its occurrence in 32 per cent of the patients. Thirty-one, or 33.7 per cent, of the 92 patients of this group studied, made a complaint of some degree of pain. It was usually in the nature of an aching, a discomfort, a heaviness, or sometimes a cramping menstrual type of pain. The pain was seldom of an intense degree. It should be remembered that early cancer anywhere does not cause actual pain. It can be readily appreciated, however, that late cancer, with metastasis, does produce definite pain and, as stressed by Healy and Brown, when the patient complains of rather persistent actual pain, metastasis or extension of the carcinoma, frequently, has occurred. Our study would tend to substantiate their observation that a definitely smaller percentage of patients are cured who complain of pain.

It is practically impossible to accurately ascertain the duration of symptoms in some cases. In some instances the first symptoms of disease were due probably to benign lesions, which later underwent malignant change. We calculated the average duration of symptoms in this group to be ten months before the patient came to treatment.

A careful physical examination is important as an aid in arriving at a correct diagnosis and often, also, in deciding the preferable plan of treatment. The size, the shape, the irregularities, and the mobility of the uterus, particularly, should be observed. It should be determined if there is either a thickening or masses in the broad ligament regions or in the culdesac, for masses may be due either to metastasis from the uterine cancer or to a benign tubo-ovarian pathologic condition. The cervix should be carefully examined, for malignant tissue or a polyp may be observed protruding from the external os. Blood

may be seen coming from the cervical canal, establishing definitely the source of the bleeding, and occasionally a metastatic malignancy will be seen on the vaginal mucosa. The incomplete physical findings, noted in some of our own records, emphasize the importance of an accurate physical examination. The physical findings, however, are essentially negative, for in about one-third of the patients with this pathologic entity, and in this group reviewed, the size of the uterus of 31 patients was considered normal. The uterus was moderately enlarged and less than the depth of six inches for 51 patients, while it was found to be markedly enlarged for ten patients.

There is only one accurate diagnostic procedure. It is a carefully performed curettement, with examination of the curettings by a competent pathologist. Sometimes, upon gently dilating the cervix, malignant tissue will begin to discharge from the uterine canal. Frequently, this will be sufficient tissue from which to make an histologic diagnosis. However, usually, a methodical curettement, with careful examination of all curettings should be done. Cautious sounding of the uterus should be made to ascertain its shape and depth. All manipulation within the uterus should be of a gentle nature in an attempt to prevent the dissemination of carcinoma cells through the lymph or venous channels or through the tubes. Irregularity of the contour is sometimes due to fibroid tumors, for these are reported present in 25 per cent, or more, of such cases. Stacy²⁰ reported fibroid tumors present in 37.23 per cent of these cases. Twenty-three of our 92 patients, or 25 per cent of this group, had fibroid tumors. Morin and Max¹² found that 35.2 per cent had fibromyomata, but only 5.6 per cent of the fibromyomata had associated cancer. While the association of fibroid tumors is not regarded as a material etiologic factor, they do, sometimes, mask the symptoms of the cancer. To conclude that all postmenopausal bleeding is due to cancer, is erroneous. Wittenbourg and Zlatmann²² collected from the literature 2,384 reports of postmenopausal bleeding. They found that the incidence of malignancy was 62.8 per cent. Unquestionably, radical surgery should not be performed with only a history of abnormal uterine bleeding. It is essential that a positive diagnosis be made first. However, caution must be exercised to the end that the bleeding due to cancer not be attributed to benign tumors. We would emphasize the importance of a thorough study of all curettings of patients with uterine fibromyomata, and furthermore, the necessity of an immediate opening and examination by the pathologist of all uteri removed for supposed benign disease. Nine patients of this group were operated upon with a pre-operative diagnosis of benign conditions, and when the uteri were opened after removal, there were found carcinomata within the fundi.

The anatomy of the uterus and the pathology of fundal cancer modify treatment. The cancers of the body of the uterus are usually adenocarcinoma. The disease is one primarily of the endometrium, therefore, at the beginning it is encased in the thick, muscle-walled cavity. There are no racemose glands extending from the endometrium into the myometrium, as are found in the cervix. The lymph supply to the fundus is sparing in nature, and the

lymphatic dissemination is late, for it is unlikely to occur until after the muscle wall has been deeply penetrated by the malignant process. Usually, the spread of the disease into and through the muscle wall is slow, requiring many months, and in some instances, years. An early case of our group emphasizes this fact. This patient had a papillary adenocarcinoma, Grade II, of the fundus, which was treated by intra-uterine application of radium. Nine years later she returned with the history of a spotting and pinkish discharge

TABLE II
DEGREE OF ACTIVITY OF
CELL MALIGNANCY

Grade	Number of patients
I	12
II	46
III	28
IV	2
Not Graded	4
65.9% were of low-grade malignancy	

TABLE III
GRADE OF MALIGNANCY IN RELATION TO AGE
AND MENOPAUSE

Grade	Average age	Pre menopause	Post menopause
I	48	6	6
II	53	13	32
III	58	3	24
IV	59	0	3

The low grade malignancies tend to occur in the younger group

for a duration of four months. On repeating the curettage the scrapings showed the same pathologic finding as they did nine years previously. Radium was again applied followed by roentgenotherapy. This patient is now apparently well, and it is two years since the last treatment. Such observations tend to support the view that a cancer of the uterine fundus often remains a local disease for many months or even a few years. It is a fortunate fact, favorably influencing treatment, that a majority of these lesions are of low grade in degree of cell activity. In this series, 58 cases, or 65.9 per cent, were found to be either Grade I or Grade II, or, approximately, two out of three of these patients had a malignancy of low degree (Tables II, III and IV).

Three methods of management used in treating body cancer are irradiation therapy, surgical extirpation, and a combination of the two. Three factors are to be carefully considered in planning treatment for an individual case. The degree of malignancy, the extent of the disease, and the physical build and the status of the general health of the individual. These three factors, together with the plan of management instituted, largely determine the percentage of cures. The extent of the disease is the most important factor modifying the results of treatment. This is true because most lesions are curable when treated early, notwithstanding the degree of cell activity or the physical status of the patient.

Practically all patients in this series have been treated by one of two methods—irradiation therapy, or the combined method of irradiation and surgery. The procedure followed, usually, was an exploratory curettage for all patients with a suspicious history with an immediate frozen-section of the curettings by the pathologist. If the microscopic examination showed the presence of a malignancy, radium was applied at the time. If the lesion was believed an operable one, and if the physical status of the patient was favorable

CANCER OF FUNDUS OF UTERUS

for surgery, usually a panhysterectomy was performed some six to eight weeks following the radium treatment. In the group of patients treated by irradiation alone, roentgenotherapy was begun two to eight weeks following the radium application, and from one to three series at two months' intervals usually were administered. For the group accepting surgery, the first roentgen

TABLE IV
CURABILITY ACCORDING TO GRADES

Grade	5-Year survival		
	Survived five years	Dead	Percent of cures
I	7	1	87.5%
II	20	15	57.4%
III	10	9	52.6%
IV	1	0	100%

The degree of malignancy definitely modifies curability

series was begun from three to eight weeks after the operation. Roentgenotherapy was used particularly to fortify against regional metastasis.

A review of these 92 cases showed that 31 patients were treated more than five years ago exclusively by irradiation therapy. Thirteen patients, or 41.9 per cent, lived from five to 13 years, however, one of these is known to have died later of cancer (Table V). Eighteen patients, or 58.1 per cent, died before the end of five years, however, two of these deaths were due to intercurrent disease. Thirteen patients have been treated within the last five years by irradiation therapy. Eight of these patients are alive to-day. Of the five dead, one lived for four years and died from diabetes. Another died within one year of an acute respiratory infection. The patients who were treated by radium and lived five years or more were given an average of 3,500 mg. hours. The patients who were given radium and lived less than five years were given an average of 3,800 mg. hours.

There were 24 patients who were treated more than five years ago by preliminary irradiation and then surgery followed by roentgenotherapy. Nineteen or 79.1 per cent, of these patients were apparently well from five to seventeen years after treatment (Table VI). Five of the 24 patients are dead, but one of the five is known to have died of an intercurrent disease. Ten patients have been treated during the last five years by this procedure, and all but one are living at this time and apparently free of disease. It is noteworthy that the highest percentage of cures has been obtained by this method of management. The statistics of these two groups would seem to support our conviction that intrauterine irradiation therapy, followed by a panhysterectomy is the preferable treatment for the patient with a carcinoma of the fundus, when the disease is still limited to the uterus, and the patient is a reasonable surgical risk. However, it is realized that a comparison of the statistics of these two methods of treatment does not give a correct evaluation

of the relative merits of the two plans of management, for a definitely higher percentage of the more favorable cases were treated by the combined procedure.

Sixty-six patients with cancer of the fundus of the uterus have been treated by various methods, treatment having been completed more than five years ago, and a study of the end-results shows that 40 patients, or 60.6 per cent,

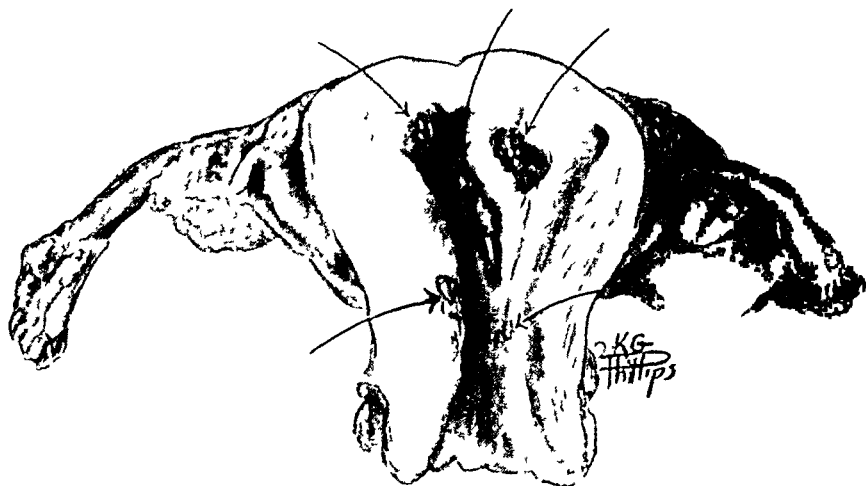


FIG 1.—Residual adenocarcinoma in fundus following 3,600 mg hrs radium eight weeks previous

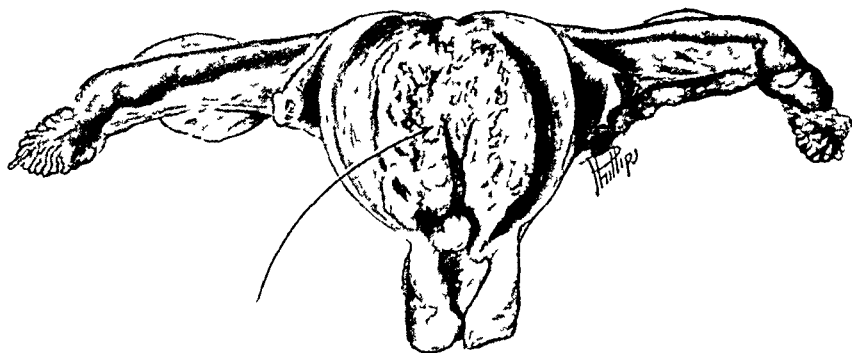


FIG 2.—Large residual adenocarcinoma in fundus following 2,400 mg hrs radium six weeks previous

lived from five to 17 years after receiving treatment. Hysterectomies have been performed for 48 patients. There was only one death, or a mortality rate of 2.1 per cent. There were no deaths from radium therapy, therefore, the mortality rate of the 92 patients treated is only one death, or 1.1 per cent.

Discussion—Thirty-four patients were given radium and later the uterus removed. A pathologic study of these uteri showed that carcinoma was still present in 18, or 55.8 per cent. No cancer cells were found in 16 specimens, or in 44.2 per cent of the removed uteri. Healy and Brown reported that cancer cells were found present in 60 per cent, or 41 of 69 uteri removed after

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irradiation therapy. However, they also found that when a large dose of radium was given, cancer cells were present in only 40 per cent of the removed uteri. Coiscaden² reported residual cancer in 61.9 per cent of the post-irradiated uteri. Sackett stated that at least one out of three hysterectomy specimens showed persistent cancer after irradiation (Figs 1 and 2). The smallest dose of radium administered to any of our patients, upon whom an hysterectomy was later performed, was 800 mg hours, and the largest dose was 4,800 mg hours. The average radium dosage was 2,600 mg hours for those uteri in which no cancer was found present, and 2,500 mg hours for those uteri in which cancer was found present. Fifteen patients have been observed more than five years who had cancer present in the removed uteri, after previous irradiation. Eleven of these patients, or 73.3 per cent, were well after five years. Nine patients have been observed more than five years who had no cancer cells present in the removed uteri, following preliminary irradiation. Eight of these nine patients, or 88.8 per cent, the dosage of radium was not standardized. It is realized, now, that a number of the earlier patients were given inadequate irradiation therapy. During the last eight years or more, the patients treated by the combined method have been given some 3,000 to 4,500 mg hours of radium preceding the hysterectomy. When the case was handled by irradiation therapy exclusively, 4,000 to 6,000 mg hours of radium were administered. This dosage was obtained frequently by giving more than one treatment. The radium was applied in tandem, the number of capsules and the length of the applicator depending on the depth of the uterus.

Technical difficulties sometimes arise in the application of radium. It is applied into an invisible field of unknown dimensions. Sampson¹⁸ has shown that the sizes and shapes of the uterine cavities are quite varied, and that, frequently, it is difficult to irradiate uniformly a malignancy of the uterine body. Usually, the patient with a small uterus can be treated satisfactorily. The large uterus requires more radium, and there is a greater element of uncertainty in its application. Therefore, inadequate irradiation is more likely to occur. Regardless of these facts, irradiation therapy has a definite place in the treatment of the corpus cancer.

Preoperative irradiation is believed to be of definite value for five reasons. Preliminary irradiation should lessen the probability of dissemination of cancer cells at the time of surgery. It may destroy some malignant tissue even beyond the scope of the surgical extirpation. It definitely lessens the probability of contaminating the field of operation with carcinoma cells. It certainly decreases the likelihood of a local or a vaginal recurrence. Since the uterine wall serves as a distance screen to the parametrial structures, a larger dose of radium can be administered before the hysterectomy than can be applied safely in the vaginal vault. For these reasons, the probability of cure is enhanced by the use of radium, preoperatively. Apparently preliminary irradiation did not materially add to the difficulty of surgery. There have been seen no

appreciable detrimental results from its use. Vaginal recurrences were developed by three of the 14 cases, upon whom hysterectomies were performed, without preliminary irradiation (Fig 3). This observation would seem to support the opinion that preoperative irradiation is of definite value.

When the uterus is moderately enlarged, due to malignant disease, there is probably an extension of the cancer to the parametrium, and these cases are

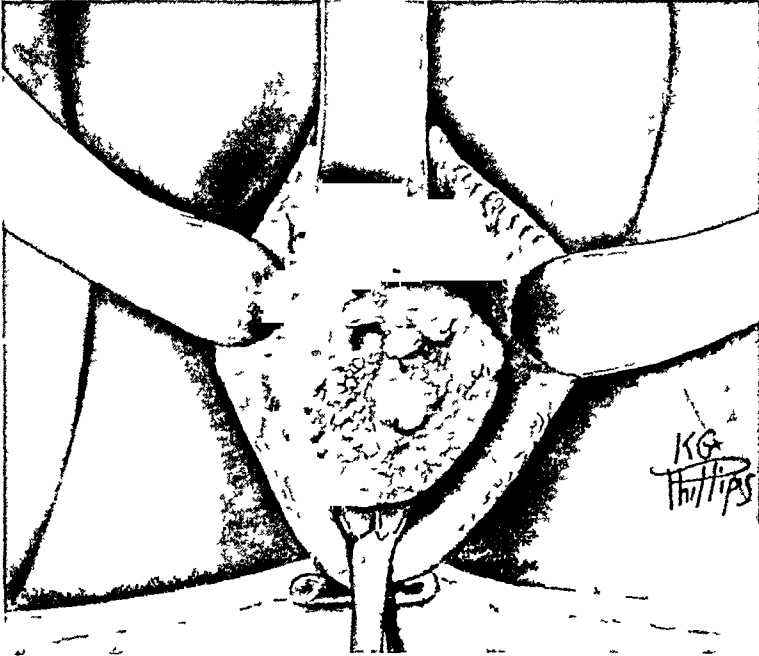


FIG 3—Vaginal recurrence four years after hysterectomy. No radiation therapy.

preferably treated by radium. However, when the enlargement is primarily due to fibroid tumors, since it is difficult to adequately irradiate such cases, these patients should have radium therapy followed by an hysterectomy. Considered as a group, the percentage of cures definitely diminishes as the size of the uterus increases. There were, in this series, ten cases who had markedly enlarged uteri, and apparently only two of the ten have been cured.

This review shows that ten patients were given irradiation therapy for a supposed benign lesion for a varying number of years preceding admission, the average being 7.7 years. Seven of these ten patients were admitted with advanced disease. This would suggest that cancer was probably present in some of the cases at the time of this previous irradiation treatment. It would also lend credence to the opinion that a number of these patients had abnormal endometria preceding the development of the corpus cancer.

It was the observation of Burnam¹ that there is a distinct tendency of these patients to develop cancer of an entirely different type in some other part of the body. Some observations noted in making this study would tend to support this point of view. There was one patient who had an adenocarcinoma of

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the fundus and, a year later, was found to have a squamous cell cancer of the cervix. Another patient had a mixed adenocarcinoma and squamous cell epithelioma of the fundus, and, a year later, she died of a sarcoma of the jejunum. Autopsy of this case revealed no evidence of a recurrence of the uterine cancer. Again, there was a patient who had a skin cancer and, five years later, adenocarcinoma of the corpus uteri, and still four years later, an

TABLE V

31 CASES TREATED BY IRRADIATION WITH A FOLLOW UP OF FIVE YEARS OR MORE

Survival	Number of patients
1 Year	5
2 Years	9
3 Years	3
4 Years	1
5 to 13 Years	13 or 41.9 %

TABLE VI

24 CASES TREATED BY PRELIMINARY IRRADIATION AND SURGERY WITH A FOLLOW UP OF FIVE YEARS OR MORE

Survival	Number of patients
1 Year	2
2 Years	1
3 Years	1
4 Years	1
5 to 17 years . . .	19 or 79.1 %

early malignancy of the rectum. Another had a skin cancer at the time of the uterine malignancy. One patient had a breast removed for a malignancy two years before admission with the fundal cancer. Still another patient had two primary cancers of the fundus which had begun in separate polyps. One of these was a Grade I malignancy, and the other, Grade II.

CONCLUSIONS

The treatment of the patient with carcinoma of the fundus uteri should be individualized, for each case must be considered from several different points of view. The cardinal symptom of this pathologic entity is a small amount of irregular bleeding. There is only one accurate diagnostic procedure—biopsy of the uterine curettings. The majority of the carcinomata of the fundus have a malignancy of low degree of cell activity. The disease may remain local for many months or even a few years. There are three methods of treatment: Irradiation therapy, surgical extirpation, and a combination of these two methods. Proper irradiation therapy will cure a fair percentage of these patients, and this is the preferable treatment for approximately one-half of the patients with this pathologic entity. Improved technic in the application of radium may increase the percentage of patients to be treated by irradiation. Small doses of radium are inadequate. Added surgery to irradiation therapy definitely increases the probability of cure when the physical status of the patient is such that she is a good surgical risk. Surgical removal of the uterus following preliminary irradiation, in carefully selected cases, is a procedure carrying a very low mortality and gives, definitely, the highest percentage of cures.

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CHEMOTHERAPY IN OSTEOMYELITIS

In the event there is a delayed diagnosis in the seriously ill patient, the end-results obtained in the treatment of osteomyelitis may be far from encouraging, and the mortality high. An early diagnosis is important in obtaining the best results. The diagnosis having been made after a careful study, the patient is prepared and operative treatment is instituted at the site of the diseased focus.

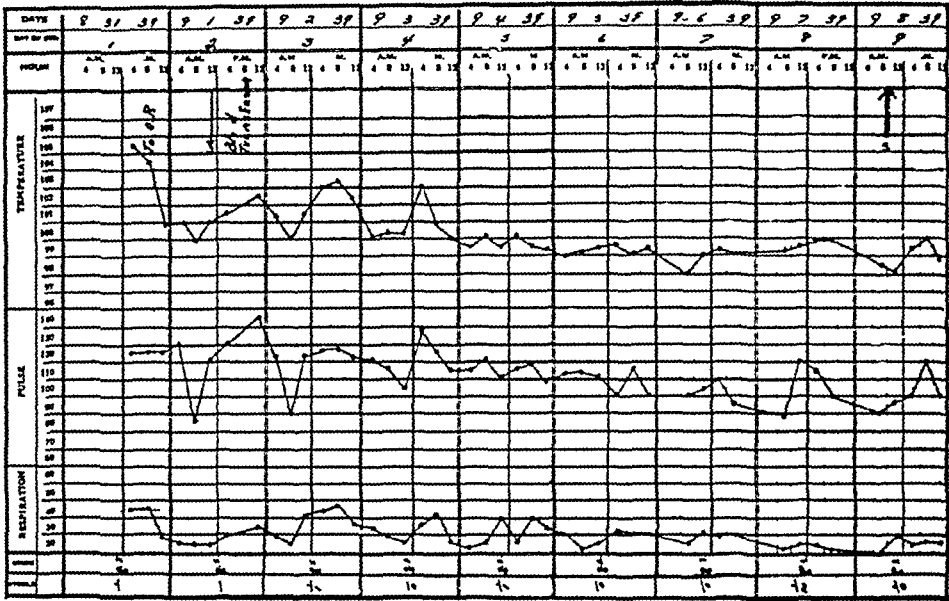


CHART 1—Case 5 Showing the temperature curve

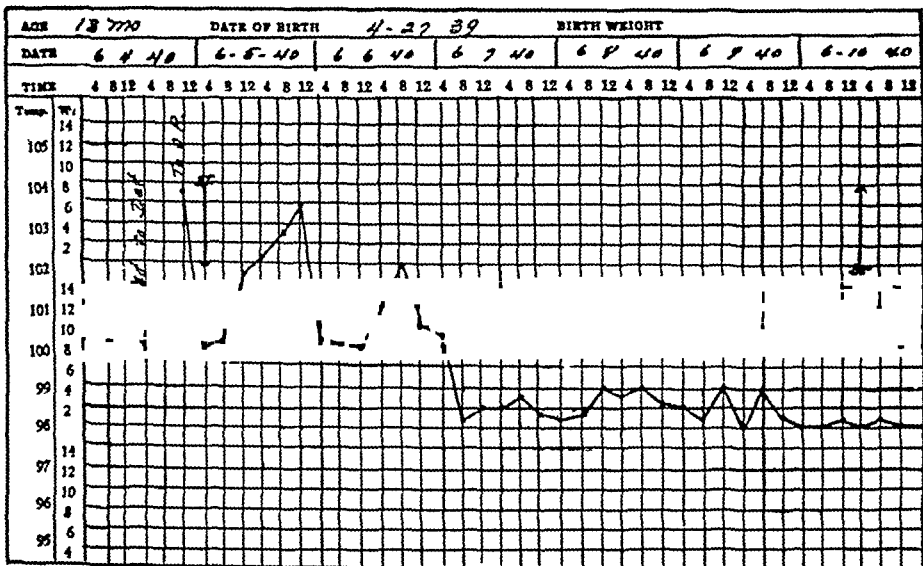


CHART 2—Case 9 Showing the temperature curve

The proper time for surgical drainage is a controversial question⁷ but, from our experience, early operative intervention combined with chemotherapy is the procedure of choice. Decompressing the shaft of the bone at the site of the lesion offers relief from pain and affords drainage, thereby minimizing the continuance of a septicemia from this focus.

The surgical procedure should be carried out with as little trauma as possible to the patient and with a minimum time for operating. The periosteum is treated gently and separated sufficiently to permit exposing the cortex over the cancellous bone which is drilled according to the usual technic. The cortex between the two or three drill-holes is removed to allow adequate drainage. Since the disease has existed for several days, the pus will usually be under such pressure as to exude around the drill before the latter is removed. The cavity is packed loosely with vaselined gauze¹⁵ and the extremity immobilized in a plaster dressing or mold. Intravenous saline and glucose solutions supplemented by small blood transfusions are given before and after operation as indicated. The surgical management of the suckling child is not as radical. The cortex of the bone in the infant is thin, and early perforation results with formation of a superficial abscess which can be drained. In the older child, the same conservative form of surgical procedure is practiced where the flat bones of the pelvis are involved, for instance, when the disease attacks the ilium, the cortex perforates early, forming a superficial abscess which may be drained. A resection of the diseased portion of the involved bone may be indicated by subsequent roentgenologic findings.

With the introduction of sulfanilamide therapy, the treatment of certain types of infection, particularly those due to the pneumococcus, meningococcus, gonococcus and certain forms of streptococci, immediately showed a high proportion of favorable results, as reported in a large number of published articles^{9, 12, 5}. However, favorable effects on infections resulting from staphylococci invasion were not apparent. Soon after the drug became available, we used it in a number of cases of acute osteomyelitis, most of which were of staphylococcic origin, and the results were discouraging. We were, therefore, forced to continue reliance on surgical drainage of local lesions, blood transfusions, and occasional antitoxin treatment for the relief of this serious disease. There was continued improvement in the mortality rate, however, many of the patients developed secondary lesions, there were many secondary operations, and often progressive bone destruction occurred, leading to long periods of morbidity and serious crippling deformities.

With some skepticism, we instituted sulfapyridine therapy, and the first patient was treated in February, 1939. Clinical investigation of this form of treatment as reported by Long,¹⁰ and others,^{11, 14} indicated a favorable effect on certain types of staphylococcic septicemia, and it seemed logical to assume that patients suffering from sepsis associated with bone infection might also be benefited (Charts 1 and 2). The results obtained with sulfapyridine therapy were encouraging from the onset and it was soon apparent that a valuable addition to the treatment of septicemia associated with staphylococcic osteomyelitis was available.

In February, 1940, sulfathiazole was supplied for experimental use in the treatment of infected bone lesions. Our results have not indicated that this preparation is more effective than sulfapyridine in the treatment of staphylococcic bone infections and the associated septicemia. The drug, however, has

been better tolerated by some of our patients, and for this reason has been substituted in practically all of our cases of this type since this therapeutic agent has been available. Practically all of the patients have tolerated sulfathiazole well and only in a few instances have gastric disturbances of any severity occurred. Dermatitis has been occasionally observed but has not been severe enough to necessitate discontinuance of the therapy. With the exception of an occasional mild hematuria, disturbances in renal function thus far has not been apparent. Acetylsulfathiazole crystals have been observed in the urine of a number of patients under treatment but have not given rise to symptoms. Cyanosis has seldom occurred and temperature reactions have not been considered a result of the administration of the drug.

Blood determination of hemoglobin, methemoglobin and sulphemoglobin have been routinely made in conjunction with blood level estimations of the drug. These studies have not indicated serious changes even when fairly high blood levels have been maintained for a number of days. Oral administration of the drug has been possible in nearly all cases. In one patient, intravenous administration of the sodium salt of sulfathiazole was necessary because of continued vomiting after oral treatment, and the drug was well-tolerated. The dosage was calculated on the basis of the patient's weight. One and one-quarter grains per pound of weight was given over a 24-hour period, divided and administered at four- or five-hour intervals. We found that this amount was usually effective, and a blood level near 4 mg per 100 cc was maintained. In cases where the blood level fell below this point the clinical response was usually satisfactory, and rarely was the dosage increased. It has not been found necessary to give large doses at the onset of the treatment, but they are usually well-tolerated and may aid in a more rapid sterilization of the blood stream by inhibiting the growth of organisms. As the patient's temperature subsided and the general condition improved, the amount of the drug was gradually reduced. Administration of this preparation was continued for several days after the temperature approached a normal level and clinical improvement was apparent.

Only recently have we considered the use of a sulfonamide derivative as a part of the local treatment of chronic osteomyelitis. During the past few weeks, following sequestrectomy and saucerization, in a number of patients with chronic osteomyelitis, we have packed the cavities with sulfathiazole powder. Insufficient time has elapsed to permit an expression of opinion regarding the value of this method of therapy. We have not employed any of these drugs locally in the cavities produced surgically in the treatment of the acute stage of the disease, although, apparently, no contraindication to such treatment exists. According to a number of published reports,^{6, 8, 3} the local use of sulfanilamide in the treatment of compound fractures has either resulted in a marked decrease in the occurrence of complicating bone infections or has aided in combating such infections when present.

Articles reporting the results from the chemotherapy type of treatment, particularly in pneumonia, predominate in the medical literature.^{4, 16, 2} Scat-

tered reports have appeared during the past year citing favorable results from chemotherapy in osteomyelitis, but, to date, we have found no record of treatment in any large series of cases. Although the series, herewith reported, is not very large, we believe a resume of our experience during the past 22 months in the treatment of this disease is justified by the results obtained.

CASE REPORTS

Case 1—A K, white, male, age 11, was admitted, February 4, 1939, complaining of pain in the left hip region of two weeks' duration. The symptoms followed a fall while tobogganing. Examination revealed an acutely ill, extremely toxic child with a rectal temperature of 103° F. There was swelling of the left hip region although the leg could be flexed at the hip joint without pain. There was great tenderness on pressure over the left ilium in the region of the anterior superior spine and considerable swelling along the iliac crest. WBC 15,800, with 80 per cent polymorphonuclears. Roentgenologic examination revealed a limited demineralization in the region of the left iliac crest. A diagnosis of acute osteomyelitis of the left ilium was made.

At operation, an abscess was found located subperiosteally and extending laterally as well as mesially to the ilium in the region of the anterior superior spine. The bone was soft and spongy and exuding purulent material. Approximately one-third of the ilium was resected subperiosteally. A culture of the exudate from the abscess gave a growth of *Staphylococcus aureus*. The postoperative course was unsatisfactory. The patient remained toxic. Blood cultures were negative. Sulfanilamide was given and small transfusions administered. The temperature declined but the patient still remained listless and appeared toxic. The administration of sulfapyridine was started in doses of 12 gr every four hours, four days after operation. The patient responded well, with a further drop in temperature to normal. He became alert and interested in his surroundings and the appetite became much improved. Swelling decreased and the amount of discharge was considerably diminished in one week. The sulfapyridine blood level was maintained between 4.8 and 8.5 mg per 100 cc for ten days, when the drug was discontinued. The patient's general condition continued to improve and he was discharged to the Convalescent Hospital in four weeks. Wound healing was complete in four months, and the patient was symptom-free.

Case 2—N P, white, female, age eight, was admitted to the Medical Service, February 11, 1939, complaining of pain in the region of the right knee of six days' duration. Examination revealed a moderately ill child, with a rectal temperature of 102° F. There was considerable tenderness and swelling just below the right knee and a possible diagnosis of osteomyelitis was considered. Hot compresses were applied and sulfapyridine administration begun in a dose of 7.5 gr every four hours. WBC 14,250, with 82 per cent polymorphonuclears. On February 15, 1939, the patient was referred to surgery. At this time, a soft tissue abscess was found below the right knee and operation was advised.

Incision down to the tibia was carried out and a trephine of the bone performed. The cortex was soft and a small amount of purulent material exuded from the drill-holes. A blood culture, taken on admission, gave a growth of *Staphylococcus aureus*, cultures of the exudate from the abscess of the leg showed the same organism. The child's temperature declined to normal in two days and the general condition improved. Sulfapyridine was discontinued on the sixth day following operation. The wound continued to discharge but in gradually decreasing amounts, while the child's general condition rapidly improved. She was discharged home on the twenty-third postoperative day. Further progress in the healing was noted on the return visits to the Out-Patient Department. A small sequestrum was expelled about six weeks following discharge, after which the wound healed rapidly. There was complete closure in five months, and the patient was walking without discomfort.

Case 3—A P, white, female, age 11, was admitted to the Medical Service, July 6, 1939, with a two-day history of pain and swelling of the right ankle, accompanied by a high fever. A tentative diagnosis of rheumatic fever was made. This child had a long previous history of pyuria with treatment in the genito-urinary clinic for over three years before this admission. Examination revealed an acutely ill child with a rectal temperature of 103° F, and swelling about the right ankle. W B C 11,500. The patient was referred to surgery eight hours after admission. The temperature at that time was 105° F, and the child had considerable pain. A diagnosis of acute osteomyelitis of the lower right tibia was made, and immediate incision and drainage was carried out, with the liberation of a large collection of pus beneath the periosteum.

The operation included a trephine of the bone and liberation of purulent exudate from the cancellous area just above the epiphysis. The administration of sulfapyridine gr 10, every four hours, was begun. There was a rapid decline in the temperature to normal in four days and the patient was sitting up and enjoying a regular diet at that time. The general condition was such that she was discharged to her home on the eighth postoperative day. A blood culture, taken on the date of admission, was reported positive for *Staphylococcus aureus* and the culture of the exudate from the operative site showed a growth of hemolytic *Staphylococcus aureus*. A blood level of sulfapyridine on the second postoperative day was 6.6 mg per 100 cc and the drug was discontinued two days later. The subsequent course has shown slow healing of the lesion. A sequestrectomy was performed six months following the initial operation and a saucerization 11 months from the date of the first operative procedure. The wound continued to heal slowly, but was completely closed three months following the last operation. Roentgenograms show satisfactory bone regeneration.

Case 4—W A, white, male, age four, was admitted, July 6, 1939, with a history of sore throat and fever one month previously. Two weeks before admission the child began to complain at night of pain just below the right knee. Swelling and tenderness of this area appeared, accompanied by a high fever. A superficial abscess of the upper right leg was incised by a physician the day before admission. The rectal temperature on entering the hospital was 101° F, and the child, though pale, weak and evidently undernourished, did not appear acutely ill. Roentgenologic examination revealed irregularity of the bone structure at the proximal end of the right tibial diaphysis. In view of the probable inadequate drainage, a further operative procedure was carried out the day following admission.

A large soft tissue abscess was opened widely and a window cut in the cortex of the upper tibia. The bone was found soft and necrotic. The wound was packed with vaselined gauze and the extremity immobilized in plaster. As a precautionary measure, sulfapyridine in doses of 7.5 gr, every five hours, was administered. Convalescence was uneventful and the child was discharged on the thirteenth day after admission. The subsequent course showed complete healing of the lesion without sequestration in four months, and there has been no reactivation of the infectious process.

Case 5—M C, white, male, age seven, was admitted, August 31, 1939, with a history of one week's duration of symptoms, including pain and swelling of the right leg. On the third day of illness, the patient was placed in a contagious hospital with a diagnosis of anterior poliomyelitis. After four days, the diagnosis of acute osteomyelitis was made and the patient was transferred to the Children's Hospital. Examination revealed a critically ill child, with a rectal temperature of 105° F. He was unconscious and practically in a moribund condition, with a barely perceptible pulse. The upper left leg was markedly swollen and discolored, and fluctuation was present. W B C 6,700, with 84 per cent polymorphonuclears.

After preparation with intravenous fluids and, as a rather desperate measure, a rapid incision and drainage of the upper right tibia was carried out. A large subperiosteal abscess was drained and a window cut in the cortex of the bone. The wound was packed open with vaselined gauze and a posterior plaster mold applied. Following operation, intravenous fluids and a blood transfusion were administered. In a few hours the oral

administration of sulfapyridine gr 15, every six hours, was begun and well-tolerated. The blood cultures on admission gave a growth of *Staphylococcus aureus*, with hemolytic *Staphylococcus aureus* recovered from the lesion of the tibia. The patient's condition following operation rapidly improved, with the temperature reaching normal on the fifth day. On the third postoperative day, the patient sat up in bed, played games and took a liberal diet. Sulfapyridine was discontinued on the eighth day following operation. The patient was discharged to the Convalescent Hospital on the eighteenth postoperative day. The subsequent course was uneventful and without further interference. The patient was sent home two months later with the wound practically healed. A month after discharge the wound was entirely healed and the patient was walking on crutches. Serial roentgenograms have shown progressive healing without evidence of sequestrum formation. When last seen, in August, 1940, there were no complaints, and the patient was walking normally.

Case 6—H. R., white, female, age two and one-half, was admitted, August 31, 1939, from the City Contagious Hospital, where she had entered the day before with a tentative diagnosis of anterior poliomyelitis. There was a history of a limp affecting the right leg following a fall one week previously. Examination revealed a critically ill child with swelling about the right hip region and pain with motion of the joint. The rectal temperature was 105° F. WBC 10,500, with 68 per cent polymorphonuclears. Aspiration of the hip joint revealed the presence of thick green pus.

After preparation with intravenous saline and glucose solution, the hip joint was entered through a posterior incision. A large amount of purulent material was evacuated. Rubber tissue drains were inserted into the joint cavity and the wound packed with vaselined gauze. A plaster hip spica was applied. A blood culture on admission and exudate from the hip joint gave a growth of *Staphylococcus aureus*. As soon after operation as possible the patient was given sulfapyridine gr 375, every four hours. This was continued for 19 days, and the blood level maintained at 35 to 37 mg per 100 cc. Four small blood transfusions were administered over a period of three weeks. The patient's general condition rapidly improved, and the temperature gradually declined to normal in the course of five days. There was a moderate amount of purulent discharge from the operative wound, gradually decreasing and on the thirty-sixth postoperative day, the patient was discharged to the Convalescent Hospital. Due to poor home conditions the patient has been kept at the hospital, although the wound has been healed for several months and roentgenograms show advanced healing of the lesion of the neck of the femur.

Case 7—A. P., white, girl, age four, was admitted, January 29, 1940, with a history of pain and swelling about the right knee over a three-day period. Examination revealed an acutely ill child with a rectal temperature of 103° F., and pain and swelling in the region of the right knee joint and the lower third of the right thigh. WBC 15,800, with 86 per cent polymorphonuclears. The right knee joint was aspirated shortly after admission and a few cubic centimeters of cloudy fluid obtained. This fluid gave a positive culture of *Staphylococcus aureus*. A blood culture taken on admission showed hemolytic *Staphylococcus aureus*.

After preparation with intravenous fluids a large subperiosteal abscess of the lower right femur was drained. A fenestra was placed in the cancellous bone just above the epiphyseal cartilage. The wound was packed open and immobilized with a heavy posterior plaster mold. Purulent exudate from the abscess yielded a growth of *Staphylococcus aureus*. A few hours after operation, sulfapyridine was given orally in doses of gr 75, five times daily. The blood level was maintained from 5 to 6.5 mg per 100 cc for nine days. The patient's condition appeared satisfactory and the temperature was normal on the seventh day after operation. At the request of the clinical bacteriologist of the hospital, sulfathiazole was substituted for the sulfapyridine on the ninth day and given in doses of 75 gr, five times daily. The temperature rose to 103° F rectally two days later, then declined and remained normal. The patient was discharged to the Convalescent Hospital on the twenty-third day following operation, with the extremity immobilized in a plaster spica dressing. The general condition has remained excellent and bone regenera-

tion has been gradual. There has been no evidence of sequestrum formation. Recent roentgenograms showed narrowing of the joint space of the right knee and demineralization of the bone structure about the joint. At present, November 11, 1940, there is an intermittent discharge of small amounts of purulent material from the operative wound.

Case 8—L. A., white, female, age six, was admitted, April 20, 1940, with a history of pain and swelling of the left leg, persisting over a period of two weeks. Examination revealed an acutely ill child with a rectal temperature of 103° F. The upper one-half of the left leg was greatly swollen and markedly tender. Fluctuation was present. Roentgenologic examination revealed characteristic signs of an acute osteomyelitis of the upper left tibia. WBC 27,600, with 68 per cent polymorphonuclears. A blood culture taken on admission gave a growth of *Staphylococcus aureus*.

The operative procedure consisted of drainage of a large soft tissue abscess and a trephine of the shaft of the tibia. A fairly large fenestra was cut in the cortex and considerable thick purulent material was evacuated from the medullary canal. The wound was packed open and a heavy posterior plaster mold applied. Cultures of the exudate from the abscess gave a growth of *Staphylococcus aureus*. Within a few hours after operation, the patient was able to take sulfathiazole in doses of 12 gr., every four hours. A blood transfusion was given the following day. The temperature subsided promptly to normal on the third day following operation, and remained normal until discharge to the Convalescent Hospital on the eleventh postoperative day. A blood culture on the eighth postoperative day gave no growth. Sulfathiazole was discontinued on the ninth day after operation. A blood level of 3.2 to 4.3 mg. per 100 cc. was maintained throughout administration.

Subsequent progress was satisfactory, with rapid subsidence of discharge and marked improvement of the patient's general condition. Roentgenologic examination two months after operation revealed a number of small sequestra, and these were removed June 22, 1940, without any attempt at extensive saucerization. The wound healed completely within eight weeks, and the patient was allowed to walk on crutches. On examination, November 1, 1940, there were no symptoms and no signs of reactivation of the inflammatory process.

Case 9—O. R., white, male, age 13 months, was admitted, June 4, 1940, with a history of refusal to use the right leg for two and one-half weeks. Swelling in the right hip region accompanied by a high fever had been present for a three-day period before admission. The patient was treated at the hospital two months previously for bronchopneumonia. Examination revealed an acutely ill child, with a rectal temperature of 104° F. The right hip was held flexed and externally rotated. There was considerable swelling about the hip region, and pain with attempted movement. Roentgenologic examination confirmed the diagnosis of an osteomyelitis of the neck of the right femur, and subluxation and lateral displacement of the femoral head was noted. WBC 24,800, with 78 per cent polymorphonuclears. Unfortunately a blood culture was not taken.

A few hours after admission, and following preparation with intravenous fluids, drainage of a large submuscular abscess posterior to the right greater trochanter was carried out, together with incision of the hip joint and evacuation of a considerable amount of purulent material. A culture of the pus from the joint gave a growth of hemolytic streptococci. The wound was packed and a plaster hip spica applied. Sulfathiazole in doses of 7.5 gr., every eight hours, was given orally following reaction from the anesthetic, and was well-tolerated. The dosage was changed to gr. 3.75, every four hours, the following day. The sulfathiazole blood level was 8.8 mg. per 100 cc. after the administration of several doses but fell to 1.4 mg. two days later. The temperature dropped rapidly to normal within 50 hours and remained at this level. Sulfathiazole was discontinued on the sixth postoperative day. The amount of discharge from the incision decreased gradually. The patient was discharged to the Convalescent Hospital on the tenth postoperative day. Healing of the lesion in the femur has progressed gradually, and the general condition has been satisfactory. Roentgenologic examination, October 2, 1940,

showed resolution of the inflammatory process and a decrease in the lateral displacement of the femoral head

Case 10—E F, white, female, age six, was admitted, June 4, 1940, with a history of pain and swelling of the lower left leg of 24 hours' duration. The symptoms occurred a few hours after a fall from a swing. Examination revealed an acutely ill girl with a rectal temperature of 105° F. The lower left leg was swollen and very tender over the lower one-third of the crest of the tibia. WBC 9,200, with 64 per cent polymorphonuclears.

Intravenous fluids were administered, following which incision and drainage was carried out and a fenestra placed in the cortex of the lower left tibia. No frank pus was encountered at any point but there was considerable edema of the soft tissues. The wound was packed and partially closed by sutures. A posterior plaster mold was applied. A culture of material from the cancellous bone gave no growth while a culture of fluid from the soft tissues gave a growth of *Staphylococcus aureus*. No blood cultures were taken. Although the findings at operation were not significant of a clinical osteomyelitis, the extreme bone tenderness, together with roentgenologic findings five days after operation indicating a pyrogenic inflammatory process, appeared to justify a diagnosis of early osteomyelitis. The patient was given 30 gr of sulfapyridine as soon as she reacted, and this was followed by doses of 15 gr, every six hours. She was given a blood transfusion on the second postoperative day. The temperature dropped rapidly to normal on the second day following operation, and was maintained at this level until discharge from the hospital. Sulfapyridine was discontinued on the third postoperative day because of the patient's rapid improvement. She was discharged on the twelfth postoperative day. The wound discharged very small amounts of seropurulent material, and healed entirely in six weeks. The patient discontinued the use of crutches, August 30, 1940, 12 weeks following operation. When seen, October 18, 1940, there were no symptoms, and the patient was walking normally.

Case 11—P G, white, male, age four, was admitted to the hospital, February 22, 1940, with a history of upper respiratory infection two weeks previously. Six days before admission he complained of a sore throat, fever and pain in the left knee. Examination showed an acutely ill child with a rectal temperature of 101° F. The left knee was swollen and there was evidence of an effusion in the joint. WBC 19,400, with 82 per cent polymorphonuclears. Blood culture, February 22, showed *Streptococcus haemolyticus*. Sulfanilamide gr 30 was given on day of admission, and gr 7.5, every six hours, thereafter. Blood level was 4.5–11.4 mg. Aspiration of the left knee joint, February 27, revealed cloudy fluid, which on culture showed *Streptococcus haemolyticus*. The temperature remained normal but there was a localized area of tenderness over the lower third of the femur. On March 5, 1940, a trephine of the cancellous portion of the femur was performed, a small amount of pus being obtained. The cortex was removed between the drill-holes, and the wound packed lightly with vaselined gauze. A posterior mold was applied. The pus on culture revealed *Streptococcus haemolyticus*. Sulfanilamide was continued postoperatively, and the level maintained at 10.6–11.8 mg, it was discontinued entirely March 17. His convalescence was rapid and he was discharged from the hospital March 23. The wound was completely healed one month after discharge and follow-up, six months later, revealed child had complete range of motion of the knee joint.

Case 12—M B, white, female, age 13, was admitted to the hospital, November 4, 1940, with a history of severe pain in the left leg of six days' duration. Examination revealed an acutely ill child, with a rectal temperature of 101° F. There was exquisite tenderness over the upper third of the left tibia. WBC 15,450, with 82 per cent polymorphonuclears. A diagnosis of acute osteomyelitis was made, and four hours after admission temperature was 104° F.

An immediate incision and drilling of the left tibia with removal of the cortex between the drill-holes was carried out just below the epiphysis, and free pus escaped along the drill. The wound was lightly packed with vaselined gauze and the leg immobil-

CHEMOTHERAPY IN OSTEOMYELITIS

ized in a posterior plaster mold Sulfathiazole, gr 30 was given every four hours, beginning the first postoperative day The blood sulfathiazole level, November 7, was 3.1 mg The temperature gradually approached normal and remained entirely normal after November 13 Three transfusions of 250 cc were given during the postoperative period Culture of the pus from the tibia revealed *Staphylococcus aureus haemolyticus* Drainage from the wound was quite profuse for the first week postoperatively but gradually dimin-

TABLE I
A Study from February, 1939 to December 1, 1940

ACUTE OSTEOMYELITIS TREATED OPERATIVELY AND WITH SULFONAMIDE COMPOUNDS

CASE	SEX	AGE	ILLNESS BEFORE ADMIT	TEMP	FOCUS	OPERATION	BACTERIOLOGY		HOSP	THERAPEUTICS	END RESULT
							WOUND CULTURE	BLOOD CULTURE			
A.K.	M.	11	14 DA.	103°	LF ILEUM	YES. RESECTION OF PORTION	STAPH. AUREUS	—	28 DA.	SULFANILAMIDE 4 DAYS SULFAPYRIDINE 10 DAYS	GOOD
M.P.	F.	8	6 DA.	102°	RT TIBIA	YES. FENESTRA	STAPH. AUREUS	+	23 DA.	SULFAPYRIDINE 8 DAYS AFTER OPERATION	GOOD SMALL SEQUESTRUM DISCHARGE
A.P.	F.	11	3 DA.	105°	RT TIBIA LOWER	YES. FENESTRA	STAPH. AUREUS HEMOLYTICUS	+	8 DA.	SULFAPYRIDINE 8 DAYS	GOOD SAUCERIZATION 11 MONTHS
W.A.	M.	4	14 DA.	101°	RT TIBIA	YES. FENESTRA AND DRA. OF ABSCESS	NO RECORD	NO RECORD	13 DA.	SULFAPYRIDINE 5 DAYS	GOOD 4 MONTHS
M.C.	M.	7	7 DA.	105°	RT TIBIA	YES. FENESTRA	STAPH. AUREUS HEMOLYTICUS	+	18 DA.	SULFAPYRIDINE 8 DAYS	GOOD
H.R.	F.	2½	7 DA.	105°	RT FEMUR NECK	YES. DRAINAGE OF JOINT	STAPH. AUREUS	+	36 DA.	SULFAPYRIDINE 19 DAYS	LESION TREATED 1 YR.
A.P.	F.	4	3 DA.	103°	RT FEMUR LOWER	YES. FENESTRA	STAPH. AUREUS	+	23 DA.	SULFAPYRIDINE 9 DAYS SULFATHIAZOLE 11 DAYS	STILL SOME DISCHARGE NO SEQUESTRUM
L.A.	F.	6	14 DA.	103°	LF TIBIA UPPER	YES. FENESTRA	STAPH. AUREUS	+	11 DA.	SULFATHIAZOLE 9 DAYS	SEQUESTRECTOMY 2 MONTHS WOUND HEALED IN 8 WEEKS
Q.R.	M.	13MO.	18 DA.	104°	RT FEMUR NECK	YES. DRAINAGE OF HIP-JOINT	STREP HEMOLYTICUS	NO RECORD	10 DA.	SULFATHIAZOLE 6 DAYS	WOUND HEALED SLIGHT DISLOCATION IMPROVED
E.F.	F.	6	1 DA.	105°	LF TIBIA LOWER	YES. FENESTRA	STAPH. AUREUS SOFT TISSUE	NO RECORD	12 DA.	SULFAPYRIDINE 3 DAYS	HEALED IN 6 WEEKS
P.G.	M.	4	14 DA.	101°	LF FEMUR LOWER	YES. FENESTRA	STREP HEMOLYTICUS	+	30 DA.	SULFANILAMIDE 18 DAYS BEFORE AND AFTER OPER.	LITTLE DRAINAGE SUPPURATIVE KNEE- JOINT SUBSIDED
M.B.	F.	13	6 DA.	102°	LF TIBIA UPPER	YES. FENESTRA	STAPH. AUREUS HEMOLYTICUS	—	16 DA.	SULFATHIAZOLE 9 DAYS AFTER OPERATION	GOOD LITTLE DISCHARGE
G.H.	M.	6	11 DA.	102°	RT FEMUR LOWER	YES. FENESTRA	STREP HEM ALSO IN KNEE-JOINT	—	35 DA.	SULFATHIAZOLE 13 DAYS	GOOD FOR OSTEO. LIMITATION OF MOVEMENT IN KNEE JOINT
G.K.	M.	2½	2 DA.	104°	LF FEMUR LOWER	YES TREPINE	STREP HEM ALSO IN KNEE JOINT	NO RECORD	12 DA.	SULFATHIAZOLE 12 DAYS	IMPROVED STILL IN HOSPITAL

ished, and the patient was allowed up in a wheel chair, November 12, and discharged from the hospital November 20

Case 13—G. H., white, male, age six and one-half, was admitted to the hospital, April 28, 1940, with a history of pain and swelling in the right knee and thigh for 11 days The latter symptoms followed an upper respiratory infection of three days' duration Examination revealed an acutely ill child, with tenderness over the lower third of the right femur, and evidence of fluid in the right knee joint Rectal temperature was 102.4° F W B C 20,800, with 90 per cent polymorphonuclears

Four hours after admission, under general anesthesia, the right knee joint was aspirated and cloudy fluid obtained An incision was then made over the lateral aspect of the right femur, drill-holes were made in the cancellous portion, and some thin pus obtained The cortex between the drill-holes was removed and the wound packed lightly with vaselined gauze The leg was immobilized in plaster Cultures from the right femur

and knee joint revealed *Streptococcus haemolyticus*. A blood transfusion was given, April 30, and the temperature ranged from 101° to 103° F. Sulfathiazole gr 15 was given, May 1, and repeated every four hours, the blood level, May 4, was 40 mg. The general postoperative course was smooth except for occasional temperature rise to 100° F. He was discharged from the hospital June 2. He was readmitted, June 19, because of swelling and pain in the right knee joint and the traction applied in extension. On June 21, aspiration of fluid from the right knee joint was attempted but none was obtained. The wound in the thigh was healed June 12. Local heat and traction were continued and the patient was discharged home, June 26, with a brace. He was readmitted, September 28, and, under general anesthesia, manipulation revealed full extension and 90° flexion. He was last seen on November 25, at which time there was evidence of thickening of the joint capsule, complete extension but flexion limited to 20°.

Case 14—G K, white, male, age two and one-half, was admitted to the Medical Service, November 21, 1940, with a history of pain in the left knee of two days' duration. A high fever had been present since the onset of the illness, and swelling of the knee had developed several hours before entering the hospital. Examination revealed an acutely ill child with a rectal temperature of 103.8° F. The left knee was moderately swollen and very tender to palpation. The joint could be moved through a range of 45° without pain. WBC 23,600, with 72 per cent polymorphonuclears. The patient was referred to the Surgical Service, November 23. At this time, the swelling of the knee was still present and, in addition, there was localized tenderness and moderate swelling over the lower one-third of the left femur. Immediate operation was advised.

The knee joint was aspirated and 4 cm of thin cloudy fluid obtained. A lateral incision was made over the lower left femur. The periosteum was incised, and drill-holes placed through the cortex. A small amount of cloudy fluid exuded from the lower drill-openings. The wound was partially closed after packing with vaselined gauze, and a posterior plaster mold applied. Cultures of the fluid from the knee and from the drill-holes in the femur both gave a growth of *Streptococcus haemolyticus*. Sulfathiazole gr 15 was given shortly after admission, continued in doses of 7.5 gr, every four hours, and was well-tolerated. The temperature declined to normal in 48 hours, and has remained at that level. The patient's general condition has greatly improved and there has been no complaint of pain since operation. On December 2, 1940, the patient was sitting up in bed and taking a regular diet. There was a moderate amount of seropurulent drainage from the wound. The sulfathiazole was discontinued on the twelfth day following admission.

The following cases are considered as a separate group because of a question in diagnosis, because of the presence of a complicating condition, or because of a change from the usual routine of treatment. These histories are not complete but are included because they represent added experience with chemotherapy in a varied number of bone and joint lesions.

Case 15—E W, male, age nine, was admitted, May 13, 1940, with a history of pain in the upper right arm of one week's duration. Examination revealed an acutely ill child with a rectal temperature of 103° F. The right shoulder was markedly swollen and painful to palpation.

Incision and drainage of the right shoulder joint was carried out shortly after admission, and a large amount of pus evacuated. Purulent exudate was found subperiosteally in the upper humerus, and drill-holes were placed into the cancellous portion of the bone. No pus was noted after trephining. The arm was immobilized in a plaster shoulder spica, in a position of abduction. Sulfathiazole was given in doses of 30 gr, four hours apart, for a total of 60 gr, and then administered in doses of 15 gr, five times daily. Intravenous fluids and a blood transfusion were given. Convalescence was uneventful. The temperature reached normal in 48 hours, and the patient's general condition improved rapidly.

Sulfathiazole was discontinued on the eighth postoperative day, and the patient was discharged on the thirteenth day after operation. The wound was completely healed in four weeks. On examination, three months after operation, there was a complete range of motion in the shoulder joint.

Case 16—D C, white, female, age six, was admitted to the Medical Service, March 27, 1939, with a diagnosis of acute rheumatic fever. Localizing symptoms developed in the right hip region several days later and the patient was transferred to the Surgical Service. A blood culture was positive for *Streptococcus haemolyticus*. Treatment consisted of immobilization with plaster, and sulfanilamide in doses of 10 gr, every six hours, over a period of 37 days. A soft tissue abscess developed in the right groin and was drained. A number of blood transfusions were administered. Roentgenologic studies showed progressive destruction of the head and neck of the right femur and the acetabulum. Soon after admission a serious cardiac lesion developed. Recovery has been slow, and the patient has been continuously immobilized during the interval of 19 months since admission in plaster spica dressings. There is considerable discharge from the sinus in the right groin at present. Recent roentgenologic studies showed some healing of the bone lesion, and evidence of beginning ankylosis. The patient's general condition is improved although there has been little change noted on repeated examinations of the heart.

Case 17—B R, white, female, age three, was admitted, September 10, 1940. The patient had been operated upon elsewhere, one year previously, and a soft tissue abscess of the upper right leg was drained. The wound has drained intermittently since. The day before admission, the leg became swollen and tender and the patient had chills and fever. On examination, there was considerable swelling and tenderness over the lateral aspect of the upper right leg. Roentgenologic study showed an extensive osteomyelitic process of the upper portion of the shaft of the right fibula.

At operation, the upper fibula was found necrotic and a considerable portion of the shaft was excised subperiosteally. The wound was partially closed and then packed with vaselined gauze. A posterior plaster mold was applied. Sulfathiazole was given in doses of 12 gr, every five hours. The child's general condition rapidly improved. The rectal temperature dropped from 103° F on admission, to normal in 24 hours, and remained at that level. The patient was discharged on the twelfth postoperative day, with the wound discharging a small amount of purulent material. On November 1, 1940, the wound was nearly healed. The patient's general condition was excellent, and roentgenograms showed evidences of healing.

Case 18—L B, white, male, age four, was admitted, August 18, 1940 with a history of pain and swelling of the upper left leg over a period of four weeks. The patient had a cold just prior to the onset of pain in the leg. The child was treated by three physicians in turn and finally sent to the hospital. One physician had incised a soft tissue abscess of the upper right leg. Examination revealed swelling and tenderness of the upper one-half of the left leg. The temperature was normal. Roentgenograms showed a diffuse destructive process of the tibial diaphysis characteristic of osteomyelitis. With bed-rest the pain and tenderness subsided and the child was transferred to the Convalescent Hospital six days after admission. He was readmitted seven days later acutely ill, with a recurrence of pain and tenderness in the left leg and a rectal temperature of 104° F. A blood culture was positive for *Staphylococcus albus*. Hot compresses were applied to the leg, and sulfathiazole administered in doses of 7.5 gr, every four hours. The temperature subsided to normal in 24 hours, and the local symptoms in the leg rapidly disappeared. The temperature remained normal and the general condition of the patient was much improved. The child was discharged on the fourteenth day after admission. Since discharge, the patient has been observed at weekly intervals. The leg remains somewhat swollen but not tender. Roentgenograms show extensive periosteal proliferation and development of a large sequestrum. Operative measures, to include sequestrectomy and saucerization, will be carried out at an early date.

Case 19—J S, white, male, age nine, was admitted to the Medical Service, June 27, 1940, with a history of pain in the region of the left knee for a period of three days. Examination revealed an acutely ill child, with a rectal temperature of 104° F. The left knee was swollen and there was pain on pressure over the lower left femur. The blood



FIG 1—Case 2 Radiograms of N P (A) March 8, 1939 (B) February 19, 1940

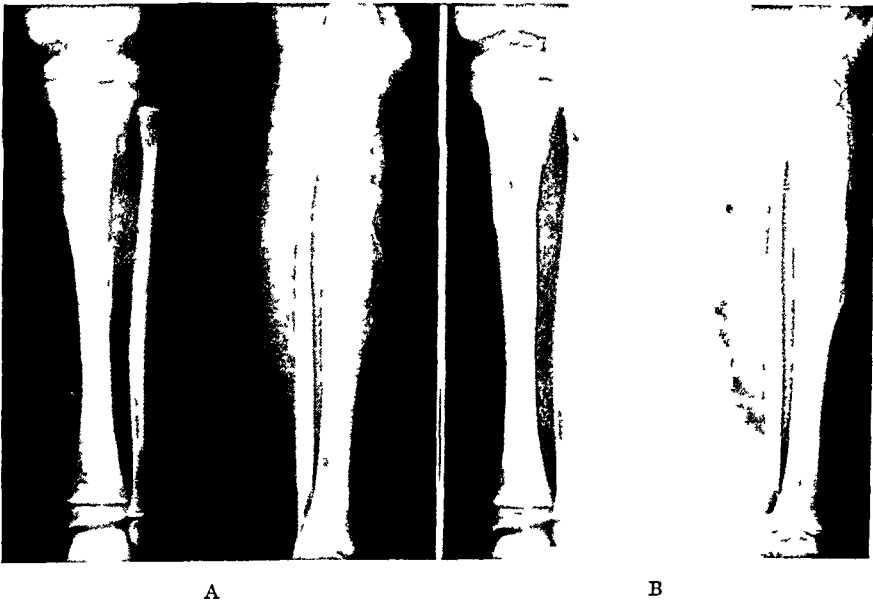


FIG 2—Case 5 Radiograms of M C (A) October 27, 1939 (B) January 12, 1940

culture was positive for *Staphylococcus aureus*. After consultation, the patient was transferred to the Surgical Service and operation performed.

The knee joint was aspirated and a small amount of cloudy fluid obtained. The lower left femur was then drilled and pus escaped from the lower openings. A culture of the fluid from the knee, and pus from the femur, gave a growth of *Staphylococcus aureus*. Sulfathiazole gr 15, five times daily, was administered, and continued in gradually decreasing

ing doses for 21 days. The temperature fell rather slowly to normal, however, the patient's general condition rapidly improved. The swelling of the knee subsided in a few days, while at no time was there more than a small amount of discharge from the incision of the lower thigh. The patient was discharged on the twenty-third postoperative day. Some swelling of the knee has recurred since discharge and there is some limitation of motion. The surgical wound is healed. Roentgenograms show normal articular cartilage spacings of the knee joint, and some demineralization of the lower femur. There are no



FIG 3—Case 5. End result in M C (ref Fig 2A and B), November 22, 1940



FIG 4—Case 1. End result in A K, December 27, 1939

definite areas of bone destruction. On November 1, 1940, the child was walking on crutches and receiving physiotherapy treatments. His general condition was satisfactory.

The foregoing discussion and the case reports emphasize the value of chemotherapy in the management of acute osteomyelitis. The histories indicate that a number of the patients were treated before operation by some form of chemotherapy. The clinical picture of sepsis complicating osteomyelitis may be masked by previous chemotherapy, but local pain and tenderness persist. The early administration of sulfapyridine or sulfathiazole apparently controls the bacteremia and no doubt plays a prominent rôle in the prevention of secondary metastatic foci in other bones. In this series, treated by chemotherapy, none of the patients developed evidence of other bone involvement (Fig 1, A and B—Fig 2, A and B). It will also be noted that only two of the cases showed evidence of later sequestration.

It is interesting to note that Brown,¹ in 1939, reported the mortality of 160 cases of acute osteomyelitis, studied in seven hospitals, and found a 11.1 per cent mortality when surgery was delayed. Practically all of the cases in our series fall in the group classified as having had delayed operation. Brown further reports that operations performed when a blood stream infection was present, resulted in a 52.6 per cent mortality. He also found that 21.9 per cent of the patients having delayed operation showed secondary bone infection (Fig 3 and Fig 4).

It is apparent from our study that chemotherapy combined with early surgery, even in the presence of a blood stream infection, reduces mortality and lowers the incidence of secondary bone involvement (Table II and Fig 5)

TABLE II

ACUTE OSTEOMYELITIS

YEAR	NO OF PATIENTS	EXPIRED	MORTALITY RATE
1934	23	5	21.7%
1935	29	7	24.1%
1936	15	3	20.0%
1937	32	3	9.3%
1938	22	1	4.5%
1939	12	0	0.0%
JAN 1 TO DEC 1 1940	7	0	0.0%
TOTAL	140	19	13.5%

CONCLUSIONS

Our experience with chemotherapy in this series of 19 patients treated for acute osteomyelitis leads us to the following conclusions

(1) Osteomyelitis is one of the serious diseases of childhood

(2) The mortality from septicemia associated with bone infections can be considerably reduced by sulfapyridine or sulfathiazole therapy, employed in conjunction with relatively early and adequate surgical drainage of the local lesion

(3) The use of these drugs aids in limiting the amount of bone destruction and deformity, helps, apparently, in the prevention of secondary metastatic lesions, and favorably influences all types of complications in number and severity

STUDY OF 140 PATIENTS WITH ACUTE OSTEOMYELITIS 1934-40

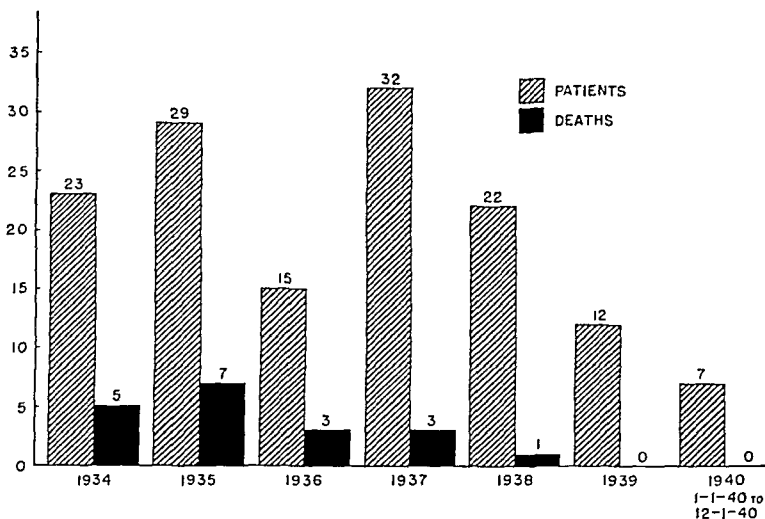


FIG 5

(4) Bone regeneration progresses more rapidly where this type of therapy is utilized, and ultimate healing occurs at an earlier date, thereby materially shortening the convalescent period

Appreciation is expressed to Clifford D. Benson, M.D., for assisting in collecting some of the data.

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DISCUSSION—DR. FRANK DICKSON (Kansas City, Mo.) Fracture of the neck of the femur has been described as the unsolved fracture, and it might with equal truth, be said that hemorrhagic osteomyelitis might be described as the unsolved disease of bone. In the future, however, through the use of chemotherapy, it seems probable that we are going to have a different picture. Doctor Penberthy has presented a series of cases in which chemotherapy has been employed, in which the results have been most satisfactory. I thoroughly agree with him in his position of advocating immediate drainage of an acute osteomyelitic focus. I do not believe in postponing drainage indefinitely or

not operating at all. Naturally, one does not operate upon a dehydrated child, but it does not take long, with proper treatment, to get a patient into satisfactory condition, and then drainage, in our opinion, should be instituted at once. The shortening of the healing period and the excellent results presented by Doctor Penberthy, in his series, makes it one of the best end-result reports in the treatment of osteomyelitis with which I am familiar.

We have had some tremendously interesting experiences with osteomyelitis, acute and chronic, using chemotherapy in the last few months. We have used sulfathiazole exclusively. Instead of packing the wound with vaselined gauze after drainage, we have placed sulfathiazole crystals in the wound and closed it up tight. All have healed by primary union—not one has broken down! We have given sulfathiazole by mouth, when possible, before operation, and for as long as 18 days following operation, as well as introducing it into the wound. The results have been primary healing, and no mortality. If the results of the use of chemotherapy continue as promising as they are at the present time, I believe that we may look upon it as a boon in the treatment of this disease which, as Doctor Penberthy says, has, heretofore, left behind it a trail of more or less incapacitated and crippled individuals.

This paper was read before the Fifty-third Annual Session of the Southern Surgical Association, Hot Springs, Va., December 10, 1940.

BRIEF COMMUNICATIONS AND CASE REPORTS

DUODENAL RUPTURE AND FAT NECROSIS

REPORT OF TWO CASES

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DUODENAL RUPTURE, uncomplicated by gross injury to other abdominal organs, is rare, as is also pancreatic rupture. The two cases herewith reported concern duodenal rupture with fat necrosis but without evident pancreatic injury.

CASE REPORTS

Case 1—A male, age 57, was admitted to the Surgical Service, Kings County Hospital, at 2 P.M., October 23, 1936, with a history of having been severely squeezed between two trucks, at the level of the lower anterior thorax and upper abdomen, at 7 A.M. of that day. He was unconscious for about an hour, then vomited—no blood.

Temperature 100° F, pulse 80, blood pressure 110/70. No evidence of peritonitis at that time. Observation was decided upon. There were 200 R.B.C. to the low power field found in the urine, and contusion of the kidney was diagnosed. The following day the temperature was unchanged, pulse had risen to 100, blood pressure 110/90. The patient was apprehensive. There was increasing abdominal rigidity, nausea but no vomiting. A plain roentgenogram of the abdomen was negative for air under the diaphragm. Perforated bowel was diagnosed and patient was operated upon.

Operative Pathology—A large amount of beef broth-like peritoneal fluid was present, and fat necrosis was noted in the upper right quadrant. The pancreas was exposed through the gastrocolic omentum and found grossly normal, nothing was found in the lesser sac. There were several contusions of the jejunum and a moderate amount of retroperitoneal hemorrhage in the right lumbar gutter. A perforation, the size of a pea, was found in the anterior wall of the third portion of the duodenum through which duodenal contents was escaping. There was no induration surrounding the perforation to indicate an old process. The area surrounding the perforation was inflamed and covered with an exudate of lymph. The perforation in the duodenum was closed with two layers of sutures. The patient became uncontrollable and eviscerated during the third day. The abdomen was resutured at once with silver wire, but he died of bronchopneumonia six days after the first operation. No autopsy was obtained. There was, however, no evidence of continuing fat necrosis at the time of the second wound closure.

Case 2—A male, age 46, was admitted to the Neurologic Service, Kings County Hospital, at 3:20 P.M., September 8, 1938, with a history of ten minutes' unconsciousness following an automobile accident. The patient was transferred to the Surgical Service after a skull fracture had been excluded. The significant findings were a small, deep laceration and contiguous brush-burn in the left upper abdominal quadrant, contusion and laceration of the forehead and lower lip, compound fracture of the mandible and nose, fracture of the left humeral shaft. The patient was treated for shock. The abdominal wall was rigid on admission, a diagnosis of lacerated abdominal viscus and hemorrhage was made, and operation was performed when recovery from shock permitted. The blood pressure at that time was 130/100, pulse 116, temperature 99° F.

Operative Pathology—Six to 700 cc of beef broth-like fluid was present in the ab-

domen, and fat necrosis was noted in the right upper abdomen and great omentum. Examination of the pancreas and its entire extent, through the gastrocolic omentum, revealed an apparently normal pancreas and an empty lesser sac. A perforation in the first portion of the duodenum, about the size of a pea, was found through which duodenal contents were escaping. There was no induration surrounding the perforation, and there was no evident effort being made to wall it off. Three layers of sutures, plus a tag of omentum, closed the perforation. Culture of the peritoneal fluid showed *Staphylococcus aureus*. The patient developed signs of peritonitis and pneumonia and died September 11, 1938, three days after operation.

Autopsy revealed general peritonitis and fat necrosis, wound infection, and a tight, sutured perforation of the first portion of the duodenum. The pancreas was apparently normal. Its ducts were not lacerated. There was bronchopneumonia. A microscopic examination of the pancreas revealed only the usual postmortem changes.

Discussion—Dragstedt, Haymond and Ellis,¹ repeated the demonstrations of previous investigators, that inactivated pancreatic juice may be poured into the peritoneal cavity without immediate serious consequences. They also showed that sterile *succus entericus*, placed in the peritoneal cavity, is relatively innocuous. When, however, infection becomes a factor, peritonitis and fat necrosis cause rapid death.

These findings are probably an adequate explanation of the foregoing cases. In one, there was no gross pancreatic injury found at operation and, in the other, no gross or microscopic evidence of pancreatic injury found at autopsy.

Boyd² notes that acute, microscopic necrosis of the pancreas may occur without gross evidence of its presence. This, therefore, may have been the condition in the unautopsied case but not in the other.

Fat necrosis consists of a breaking down of fat by means of activated trypsinogen and lipase. The trypsinogen is activated by enterokinase derived either from the *succus entericus* or from the breaking down of traumatized cells. The activated trypsinogen must get under the peritoneal covering to get at the fat cells and kill them, permitting the lipase to break down the fat into fatty acids and glycerin. The peculiar spotty appearance of fat necrosis suggests lymphatic spread, and we know that this spread may at times penetrate the diaphragm and involve the pleura and pericardium.

One wonders why, if duodenal rupture be the cause of fat necrosis at times, one does not find the condition more often. Certainly the writer has never seen fat necrosis complicating the perforation of an ordinary duodenal ulcer, and questioning of others has not elicited it as having been a factor in this condition. Certainly, it is worthy of note that the finding of fat necrosis in a traumatic abdomen should direct one's attention to the first and third parts of the duodenum if no pancreatic injury appears after exploration of both peritoneal cavities.

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TOTAL CYSTECTOMY WITH BILATERAL NEPHROSTOMY FOR CARCINOMA OF THE BLADDER

FIVE-YEAR RESULT

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Case Report—The patient, a male, age 51, was admitted to Mt Sinai Hospital, in August, 1934, with the following history. He had had gross hematuria for five months for which he was treated with bladder lavages. When he came to the hospital his urine was grossly bloody, he urinated many times during the day and ten or 12 times at night. He had lost 40 lbs of weight during the four months prior to entering the hospital. When admitted, he was in an emaciated, cachectic condition, running a temperature between 102° and 104° F. Roentgenologic examination of the kidneys was negative for calculi. Intravenous pyelography showed some dilatation of the right kidney with poor visualization, whereas the left kidney was apparently normal. Cystograms were then taken which showed a huge filling defect in the bladder, representing the tumor that was later removed. He was then cystoscoped, with difficulty, on account of the marked hematuria. This showed a tremendous neoplasm occupying the greater part of the bladder, extending down to the internal sphincter and covering over the trigonal region so that the ureteral orifices could not be visualized. A biopsy was taken from the tumor which was reported as an infiltrating squamous cell carcinoma with areas of necrosis. The patient was in such a debilitated condition nothing could be done for three or four days, except to give him several transfusions. He had no kidney tenderness, but we suspected that the temperature was probably due to infection of the right kidney. At that time his hemoglobin was 35 per cent, and he had received three transfusions.

On August 14, 1934, a right nephrostomy was performed. On opening the kidney there was escape of purulent urine. A tube was introduced through the cortex into the pelvis of the kidney. There was remarkable improvement following this nephrostomy. The temperature dropped to normal in 48 hours, and the general condition improved. He looked like a different individual. He was given small transfusions at short intervals so that, in about two weeks' time, he was in such good condition that we considered it advisable to go ahead with the second stage of the operation. After reviewing the cystograms and the cystoscopic picture we decided there was only one thing to do—total cystectomy. The tumor was too huge for radiation or partial resection, it was either do nothing at all or a total cystectomy. This was performed, August 24, 1934.

Operation—Through a midline incision, an enormous bladder was exposed, which made mobilization rather difficult despite the long incision. After tying off the vesicular arteries, the bladder was mobilized down to the prostate. The bladder, seminal vesicles and half of the prostate were removed in one piece, without opening into the bladder. The left ureter was mobilized, cut across and implanted in the anterior abdominal wall just internal to the anterior superior spine. The patient did well for two days. Then the temperature rose to 102° F. He was draining well through the right nephrostomy wound, we noticed, however, that drainage had stopped from the left nephrostomy in the skin. We found that this ureter had retracted. In view of the nephrostomy on the right side, it was thought best to perform a nephrostomy on the left side instead of another reimplantation of this ureter. This was done, and the patient improved remarkably. The temperature dropped to normal, and he was discharged from the

hospital after five weeks. Within six months he had gained 40 lbs. in weight, his hemoglobin rose from 35 to 70 per cent, and he was in excellent condition.

Subsequent Course—The patient has been followed to the present time. The post-operative treatment consisted in changing his nephrostomy tubes once every two weeks with occasional pelvic lavages. On-and-off, he has had some form of urinary antiseptics. He was well until 1936, when he was admitted for bleeding from the left nephrostomy tube. Roentgenologic examination showed no calculi. After a few pelvic lavages this stopped and he was discharged after a few days. He went along in very good condition until 1939, when he was readmitted because of trouble with the drainage through the right nephrostomy tube. Examination showed that there was a calculus in the nephrostomy sinus. This was easily removed after dilating the sinus, and he has been well ever since.

We feel that total cystectomy has a definite place in the management of certain types of bladder carcinoma, particularly extensive cancer, such as this was, in large tumors involving the neck of the bladder and the trigonal region, and those growths that, to a large extent, infiltrate from the bladder into the prostate. Our method of choice is total cystectomy with skin implantation preferably in two stages. At the first stage, both ureters are implanted in the skin, after which the bladder is removed. Most of these kidneys are infected, the ureters are generally dilated so that there is a large risk attached to performing an ureterosigmoid implantation. When dealing with non-infected kidneys and normal ureters, implantation into the sigmoid is perhaps the preferable procedure.

We have performed 27 total cystectomies to date, with an operative mortality of 22 per cent. The longest survival after an operation, such as this one, has been nine years, and this patient did not die of a metastatic lesion but of renal infection. We have patients who have survived cystectomy four, five, seven, and eight years. About 50 per cent of the patients who survived the operation have lived five years or longer.

ABSTRACTS OF PAPERS
PRESENTED BEFORE THE FIRST ANNUAL ASSEMBLY
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CARCINOID TUMOR OF THE CECUM

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ONLY 11 CASES of carcinoid tumors of the colon have been reported in five of which the lesion was in the cecum. Wyatt was able to collect reports of eight cases of carcinoid tumors of the large bowel from the literature, and reported one of his own. In three cases of this series the cecum was

tumor, cecum, and appendix were removed, and pathologic examination revealed adenocarcinoma, Grade I, of the so-called carcinoid type. The tumor measured 2 cm. in diameter and was situated in the cecum at the base of the appendix with obstruction of the appendiceal lumen (Figs. 1, 2 and 3). Ex-

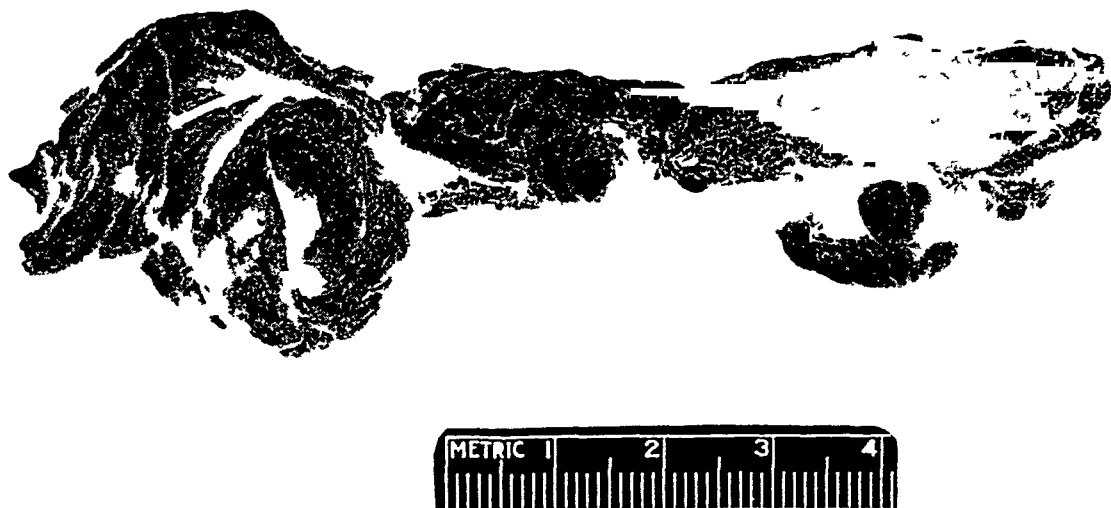


FIG. 1.—Gross specimen. Showing cecum with tumor, and its relation to appendix.

involved. Besides these three we wish to call attention to two more and to report a sixth case which makes the total number of carcinoid tumors of the colon 12. The first was reported by C. W. Mayo in 1933 and the second case has been reviewed in detail recently by Mayo and Wilson.

CASE REPORT—The patient, a female age 20, was operated upon for perforative appendicitis with peritonitis and in addition, was found to have a small tumor in the cecum at the base of the appendix. The

amination of the appendix revealed acute purulent appendicitis.

COMMENT—There are now six known cases of carcinoid tumor of the cecum. The clinical record in one is not available in two the tumors did not produce symptoms in two they caused symptoms of obstruction (one by intussusception, although it was situated at the appendocecal junction), in the remaining case the tumor was located in the cecum near the base of the appendix and caused acute obstructive appendicitis. In

only one of the six cases were the tumors multiple. In two metastasis was demonstrable. In the case we have reported no attempt was made to explore the general ab-

dominally in the base at the crypts of Lieberkuhn. They grow slowly and their relative infrequency probably will continue to prevent their preoperative diagnosis. However their



FIG 2—Showing relation on bisection



FIG 3—Photomicrograph showing pathologic characteristics of the carcinoid tumor Grade I ($\times 100$)

dominal cavity because of the peritonitis.

The tumors are thought to originate in the cells of Kulchitsky which are found throughout the gastro intestinal tract espe-

cially in the base at the crypts of Lieberkuhn. They grow slowly and their relative infrequency probably will continue to prevent their preoperative diagnosis. However their relative benignancy makes local excision feasible and any extensive type of resection seldom necessary, unless their pathologic characteristics are questionable.

THE CLINICAL SIGNIFICANCE OF HUMAN GASTRIC MOTILITY¹

Frank E. Hamilton, M.D.

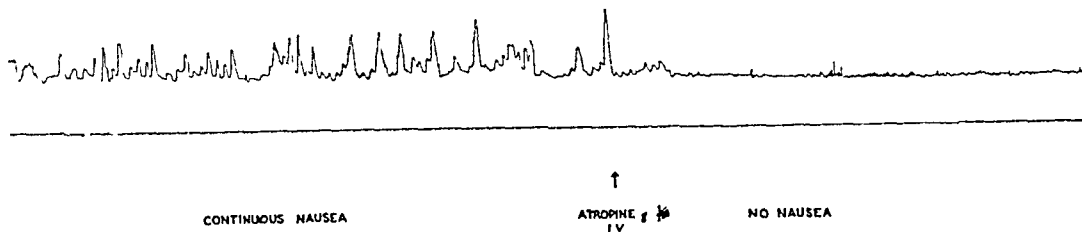
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THE MOTOR ACTIVITY of the human stomach is of demonstrable clinical importance. It is affected not only by disturbances in gastric physiology, but also by certain pathologic changes occurring elsewhere in the gastro-intestinal tract. In earlier investigations of the department^{1, 2, 3, 4, 5} the balloon and kymograph method was used to study the influence of the extrinsic innervation, the reaction of the stomach following celiotomy, and the effect of drugs upon gastric motility.

benign obstructive duodenal ulcer revealed kymographic evidence of gastric hyperactivity occurring simultaneously with clinical evidence of pylorospasm. Spontaneous hypomotility of the stomach was associated with simultaneous relief from pain. Activation of the stomach following administration of morphine or the atropine prostigmine sequence was associated with epigastric pain. Following administration of atropine or ephedrine gastric quiescence ensued and at once the pain ceased.

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ESOPHAGO-PLEURAL FISTULA
NAUSEA SIX DAYS FOLLOWING APICAL THORACOPLASTY
BALLOON INTRODUCED INTO STOMACH THRU GASTROSTOMY STOMA



GRAPH 1—The control of late postoperative nausea. Continuous nausea was observed throughout the period of gastric hypermotility. Coincident with the onset of gastric hypomotility there was complete relief from nausea.

With these studies as a background we are now investigating clinical variations in gastric motility. A patient who complained of postoperative gas pains was studied. The kymograph recorded greatly increased gastric activity coincident with clinical evidence of pain. Decreased gastric activity and simultaneous cessation of pain followed administration of atropine.

Late postoperative nausea was studied on a patient with a permanent gastrostomy. The balloon was inserted directly through the gastrostomy opening, and the stomach was found to be in constant, irregular hyperactivity. During this period the patient complained of continuous nausea. Following intravenous administration of atropine there was immediate cessation of gastric activity along with complete relief of the nausea (Graph 1).

Preoperative studies of a patient with a

The relation of gastric motility to biliary colic was investigated upon a patient who at subsequent operation was shown to have the gallbladder cystic duct, and common duct filled with small cholesterol stones. Preoperatively, the patient had occasional attacks of upper right quadrant pain, clinically indistinguishable from biliary colic. A motility investigation during such an attack revealed constant gastric hyperactivity. Administration of intravenous atropine was quickly followed by gastric quiescence and complete relief from pain. Morphine reversed the action of atropine and coincident with the pronounced irregular gastric hyperactivity the patient again complained of colic-like upper right quadrant pain indistinguishable from the pain of biliary colic (Graph 2).

From these studies it appears that gastric motility is affected by certain lesions of the

* We are indebted to Abbott Laboratories, Inc. for the intravenous preparations of atropine and morphine, also to Hoffman-La Roche, Inc., for the prostigmine used in this investigation.

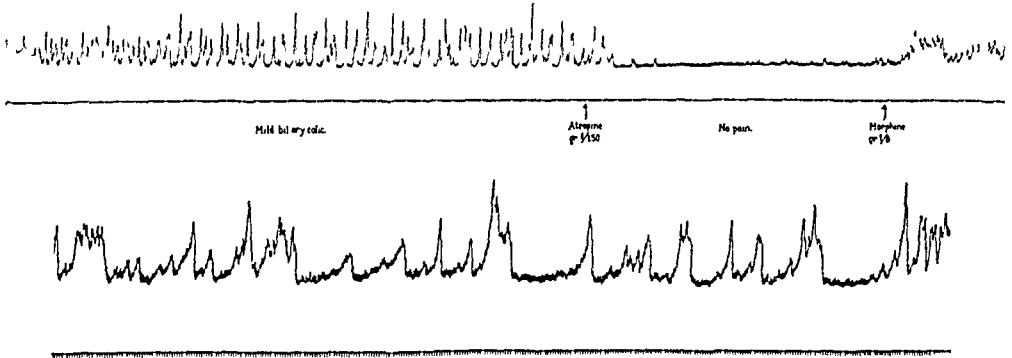
This investigation was aided by a grant from the Combs Fund for Research of the Ohio State University.

stomach as well as by certain lesions of more distal intestine similarly innervated. In the cases reported, clinical discomfort occurred simultaneously with kymographic evidence of gastric hypermotility whether that hypermotility was spontaneous or induced by the administration of morphine or the atropine-prostigmine sequence. Conversely, the pa-

of Morphine and Atropine on the Human Stomach *Jour Pharm and Exper Therap* 61, 230, 1937

⁵ Veach, Harry O, Lauer, B R, and James A G Effects of Prostigmine and Atropine on the Human Stomach *Jour Pharm and Exper Therap*, 62, 422, 1938

NK 2 6 59 Stomach.
Control of Biliary Colic.



Colic like pain

GRAPH 2—The symptomatic control of biliary colic due to cholecystitis with cholelithiasis. Continuous upper right quadrant pain, indistinguishable from that of biliary colic, was noted throughout the entire period of gastric hypermotility. Complete clinical relief was noted coincident with gastric hypomotility induced by the intravenous administration of atropine. Morphine reversed the action of atropine and with the recurrence of gastric hyperactivity the patient again complained of severe pain indistinguishable from that of biliary colic.

tients ceased to complain of pain when the stomach was quiescent whether that quiescence was spontaneous or was induced by the administration of atropine or ephedrine.

Abnormal motility of the human stomach would seem to be often associated with common abdominal disorders. Control of the abnormal gastric activity by means of standard drugs will often simultaneously control the clinical symptoms.

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- ⁴ Veach Harry O The Antagonistic Action

DISCUSSION—DR J C SCHNEDORF (Kansas City) I should like to ask Doctor Hamilton whether he has differentiated the hypermotility in the different clinical conditions of the stomach from the hypermotility of the stomach as seen in hunger contractions and whether he has tried controlled injections such as injecting saline. That certainly has a sedative effect upon the hypermotility of the stomach.

DR FRANK E HAMILTON (Columbus closing) There is very little similarity between hunger contractions and the gastric hypermotility associated with the type of gastro-intestinal disorders described in this paper. Moreover, although the gastric motility investigations are conducted under controlled conditions with an empty stomach, they are not continued until such a time as the patient complains of hunger. As a further control, whenever possible, we use intravenous drugs for immediacy of action so that if a motility change is observed it will have been clearly due to the drug action. Control injections such as intravenous saline have not altered gastric

motility if administered during a period of hypermotility due to pathologic lesions, such as biliary colic or pylorospasm

DR STUART C CULLEN (Iowa City)
I should like to ask Doctor Hamilton if he has used a combination of drugs simultaneously, such as morphine and atropine together?

DR FRANK E HAMILTON (Columbus,

closing) Yes, we have used morphine and atropine, together in the usual preoperative dosage of 1/6 grain of morphine and 1/150 grain of atropine or 1/4 grain morphine and 1/100 grain of atropine Following such an injection, gastric hypermotility is observed The hypermotility is as a rule, less marked than when morphine is administered alone, but a definite period of gastric hypermotility usually follows the injection of morphine and atropine



PERITONEAL FLUID IN PERFORATED PEPTIC ULCERS

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THERE IS fairly general agreement that intra-abdominal infection is the chief cause of death following perforation of a gastric or duodenal ulcer This is borne out by a series of 98 individuals who have had simple closure of perforated ulcers at the Receiving Hospital during the past two years Of these, ten died and eight were autopsied Six died of severe, acute diffuse peritonitis and two had large intraperitoneal abscesses The time interval between perforation and operation varied widely in this group, ranging from two to 48 hours

Our observations on a number of patients who have had simple closure of perforated ulcers, have convinced us that chemical irritation of the peritoneum is of relatively little significance in influencing the general mortality as compared with bacterial contamination

Swab cultures of the peritoneal fluid in 67 cases were productive of bacterial growth in 43 instances and negative in 24 From 34 cases, both a swab and a larger specimen usually 3 cc were separately cultured in each case This was done to determine if dilution might be responsible for some of the negative cultures Twenty-seven of the 3 cc specimens gave bacterial growth but only 19 of the swabs were positive

More recently, colony counts have been made on agar plates inoculated with 3 cc of peritoneal fluid In the few cases studied there has been a general parallelism between the duration of the perforation the volume of fluid, and the number of organisms per cubic centimeter

The bacterial organisms most frequently recovered at operation have been in order of

frequency *Streptococcus viridans* non-hemolytic streptococci, staphylococci, and *B coli*

The assumption that bacterial growth is modified by gastric secretion implies that there is a high concentration of gastric hydrochloric acid at the time of perforation Our results show that the hydrogen ion concentration of the gastric contents at the time of operation is low The individual pH values varied widely ranging from two and one-half to eight most being between pH four and eight Furthermore, we have in almost every case obtained bacterial growth from the gastric contents at the time of operation

The nature of the fluid in the peritoneal cavity was of interest to us because of its relation to bacterial growth To our surprise, we found that in almost every case, the peritoneal fluid was neutral, with a pH very close to seven The chloride content of each specimen was uniformly that of blood plasma The plasma-like character of the peritoneal fluid was constant regardless of the duration of the perforation or the volume of fluid in the peritoneal cavity

In summary, we find that micro-organisms are present in the peritoneal cavity very shortly after ulcer perforation The gastric acidity is low at the time of operation and bacteria are to be found in the gastric contents The peritoneal fluid at operation has an hydrogen ion concentration and chloride content approaching blood plasma Thus we find no evidence which would indicate modification of the activity of bacterial growth by gastric contents or by peritoneal fluid

CIRCULATION OF THE SMALL INTESTINE

A Comparison of Man with Laboratory Animals

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DETAILED STUDIES of the distribution of the superior mesenteric vessels and their branches have been made in the following animals Man dog cat rabbit opossum raccoon and a species of kangaroo The vessels have been injected with liquid latex and the specimens then fixed and cleared by a modification of the Spalteholz technic These preparations clearly demonstrate differences in the intestinal blood supply of

dog and man differences so great as to make the dog inadvisable to use as an experimental animal for studies on the effect of distention on the blood supply of the human intestine Some of the other species show a greater resemblance but the search is being continued in an effort to find a laboratory animal more comparable to man in this respect in order that experimental data may be better evaluated



NERVE COMPRESSION SYNDROME AND SURGERY FOR A CERTAIN TYPE OF SCIATIC NEURITIS

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THE CHIEF PURPOSE in presenting this paper is to call attention to a certain group of patients who have suffered for at least a number of months from a sciatic neuritis which in our experience has been found to be due not to a ruptured intervertebral disk or to hypertrophied ligamenta subflava but rather to encroachment upon the nerve or nerves by one or several of the other anatomic structures adjacent to the intervertebral foramina

We have reviewed 42 consecutive cases upon whom laminectomies were performed and who have been followed for a period of from six months to three years after operation For this paper we have focused our attention on (1) the type of lesion found (2) the extent of exploration which was performed and (3) the end-results

In this group we found only 25 per cent due to ruptured intervertebral disks and in only 7 per cent was the etiologic factor apparently thickened ligamenta subflava In the remaining 68 per cent we found the compressing or irritating factor to be one or several of the following structures (1) A narrowed intervertebral foramen (2)

a prominent but not ruptured intervertebral disk or hypertrophic arthritis (3) abnormally dilated lumbar veins accompanying the nerves into the foramina and (4) adhesions to a nerve from previous inflammation or subarachnoid alcohol injection The important feature seemed to be the combination of two or three of the encroaching factors as without this there might have been chances for compensatory relief from the pressure or irritation To designate this group of cases we have been using the term Nerve Compression Syndrome

In our experience this latter group of cases has differed from those due to ruptured intervertebral disks in that the history of trauma has been less definite and the roentgenologic evidence with air or lipiodol has been less clear-cut The history of persisting incapacitating pain the objective evidences of sciatic neuritis and the changes in the total protein of the spinal fluid have been about the same in the two groups

The extent of operative exposure that was necessary depended upon the findings With a localized protruded portion of ruptured disk a limited exposure usually suf

ficed But if this was not found we continued exposure of the nerves involved, until we were certain that all possible compressing factors were removed even including removal of overhanging borders of facets at the foramina In our experience thus far, it seems that the end-results were better where this more extensive exposure was made

The end-results in this group thus far have been very satisfactory as judged by the patients own estimate of percentage of relief of symptoms Thus far, the only poor results were with ruptured disks and of

these, two were definitely psychoneuroses associated with compensation

In summary, we wish to call attention to a group of patients with sciatic neuritis which seems to be due to a combination of pressure and irritative factors other than protruded intervertebral disks and hypertrophied ligamenta subflava

We propose the term 'Nerve Compression Syndrome' for this miscellaneous group We advocate adequate surgical removal of all or sufficient compressing factors More time must pass before we can evaluate with certainty the final end-results



RETROPERITONEAL HEMORRHAGE

With Special Reference to the Accompanying Paralytic Ileus

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RETROPERITONEAL HEMORRHAGE may be due to traumatic and nontraumatic factors It is invariably associated with a paralytic ileus Among the more common traumatic factors are direct injury to retroperitoneal tissues, fractures, and operative trauma Of the nontraumatic causes rupture of an abdominal aorta and spontaneous perirenal hematoma were most frequently encountered

Several unusual cases of retroperitoneal hemorrhage were observed at the Evanston Hospital The first case was a retroperitoneal hemorrhage following an appendectomy The source of the hemorrhage was the lateral ascending branch of the deep circumflex artery This vessel is frequently encountered and often traumatized in the course of an appendectomy through a McBurney's incision Ligation of this vessel is advised

The second case was a retroperitoneal hemorrhage into the broad ligament following a vaginal hysterectomy Recovery occurred in both cases but only after stormy postoperative courses due to paralytic ileus

Seven cases are reported of patients who died of ruptured abdominal aorta retroperitoneally The clinical findings in these patients were quite similar to those of retroperitoneal hemorrhage from other causes The syndrome often simulates a

peritonitis Severe abdominal pain followed by circulatory collapse marked pallor, and often a palpable mass with abdominal rigidity are early findings Later, within 24 hours to five days after onset of pain a paralytic ileus develops Roentgenogram of the abdomen reveals the aneurysm in 75 per cent of abdominal aneurysms

Patients with perirenal hematoma had renal pain, signs of hemorrhage and a palpable tumor

Treatment of the retroperitoneal hemorrhage depends upon the cause Prognosis was better in the traumatic group

Paralytic ileus was found frequently following a retroperitoneal hemorrhage The mechanism of the reflex seemed to be due to a paralysis of the splanchnic and parasympathetic systems and not a stimulation of the splanchnic system alone

Whatever the explanation of the physiologic processes involved may be the condition is quite serious Wangensteen suction and occasionally enterostomy have been necessary for relief of the ileus Evacuation of the hematoma only in those conditions which allowed this procedure is recommended Ligation of the abdominal aorta for aortic aneurysm before hemorrhage occurs should be attempted in selected cases In any case the prognosis should be guarded

THE PATHOGENICITY OF THE BACTERIA OF APPENDICITIS
PERITONITISWilliam A Altemeier, MD
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PERITONITIS secondary to acute perforated appendicitis is rarely caused by a single type of bacterium. On the contrary the bacterial flora of the peritonitis exudate is mixed and varied and any of the intestinal bacteria either aerobic or anaerobic, may be found.¹

In this communication the pathogenicity of these bacteria for experimental animals has been studied. The majority of the aerobic strains tested produced minor local lesions or cellulitis when injected subcutaneously but their intraperitoneal injection usually failed to cause a fatal peritonitis. The aerobes capable of producing a fatal peritonitis included some strains of *B. coli*, *B. pyocyaneus* and *B. alkaligenes*. Twenty-one strains of *B. coli* were thus tested and three of these were quite virulent producing large areas of cellulitis and rapidly fatal peritonitis. The remaining 18 produced minor local subcutaneous lesions but no fatal peritonitis.

The virulence of the aerobic bacteria particularly *B. coli* for guinea-pigs and rabbits could be greatly increased by the coincidental intraperitoneal injection of many particles of autoclaved sterile tissue through a large-bore needle. Similar observations had been made by Halsted² working with the *Staphylococcus*.

Many of the anaerobic organisms were difficult to cultivate in pure culture. By using deep tubes containing brain broth and a small amount of blood a fairly good growth was usually obtained under strict anaerobic conditions. The majority of the anaerobic bacteria investigated did not produce a fatal peritonitis with the exception of hemolytic streptococci *B. thetoides*, and *B. fragilis*. The *B. melaninogenicum* frequently found in our series¹ of peritonitic exudates, was very difficult to separate from an anaerobic *Streptococcus* with which it was frequently and intimately associated. It was found to be relatively nonpathogenic.

If several or more species of these bacteria, found in a given case of peritonitis were mixed and cultivated, simulating their ex-

istence in the peritoneal exudate, their composite virulence was greatly increased. Equal or smaller doses of the mixed cultures usually produced extensive areas of cellulitis with gangrene and overwhelmingly fatal peritonitis. The synergistic effect produced by these groups of bacteria was repeatedly demonstrated.

Symbiosis in disease has attracted relatively little attention in medicine and surgery. The fulfillment of Koch's postulates by a single species of bacteria is generally required for the establishment of the etiology of disease. In discussing the rôle of *C. welchii* in appendicitis Jennings,³ in 1923 believed that *C. welchii* infection occurred as a rule, in symbiosis with a number of other bacteria. The experiments of Weinberg, Prevot, Davesne and Renard⁴ in 1928 suggested the possibility that not only appendicitis but also peritonitis was the result of the combined action of bacterial mixtures. After studying the pathogenicity of *B. coli* nonhemolytic streptococci and *C. welchii* in pure and mixed culture Meleney, Olpp, Harvey and Jenn⁵ clearly demonstrated the synergistic activity of these three symbionts in peritonitis. In our experiments these findings have been substantiated and a similar accumulative action of many more species of aerobic and anaerobic bacteria has been shown. These experiments give credence to the previous observations that the clinical course of the illness was much more serious if more than one type of intestinal bacterium was present in the peritoneal exudate than if only one was present.

In summary an analysis of the literature and our experiments indicates that appendicitis peritonitis is usually a polymicrobial infection caused by the synergistic pathogenic action of a group of bacteria existing in a state of symbiosis. Correlation of clinical and experimental studies shows that in general, the greater the number of intestinal bacterial species present in the exudate, the greater the severity of the peritoneal infection is likely to be.

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DISCUSSION—DR ROY MCCLURE I should like to ask Doctor Altemeier whether he has done any work in connection with sulfanilamide or its derivatives, and whether it has any specific action with this group of bacteria that he has shown us

DR W A ALTEMEIER (Cincinnati closing) I have not done much work with the sulfonamides in relation to peritonitis except on a group of rabbits in which I injected lethal amounts of similar mixed cultures to those shown on the slides If I injected sulfanilamide coincidentally with the mixed cultures, the animals were saved in a large percentage of the cases—some 75 per cent, as I remember If the injection of the sulfanilamide was delayed as long as four hours after this particular mixed culture was injected, the animals never survived In the control animals 100 per cent of the animals would die after the injection So the evidence that I had pointed to the fact that in rabbits, sulfanilamide, if administered at the time of the injection or shortly after, protected the animals in a large percentage of the cases if delayed, it failed to protect them



TISSUE REACTIONS TO SUTURE MATERIALS

A Preliminary Report

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METHODS OF STUDY—A series of experiments have been carried out utilizing the anterior chamber of the rabbit's eye in an effort to standardize the effects of trauma, tension, and hemostasis The fact that the anterior chamber of the eye is an excellent culture medium is apparent from the ease with which tissue cultures and experimental neoplasms may be grown in this site Small segments of suture material placed in the anterior chamber may be observed grossly through the transparent cornea, and cell counts made of the aqueous humor at varying intervals may be taken as a quantitative index of the reaction One centimeter segments of catgut, silk, stainless steel wire, nylon, silkworm catgut, and ordinary spool cotton have been placed in the anterior chamber under aseptic technic

In an effort to determine whether catgut might possess antigenic propensities another series of animals have been sensitized to

sheep serum and catgut introduced into the eye subsequently Employing the usual hemacytometer, cell counts have been made at varying intervals and cultures of the aqueous humor taken

Results—The marked difference in the reaction between the absorbable and non-absorbable sutures is strikingly apparent when this method of study is employed In general, the reaction to silk is very minimal For the first seven days there is practically no reaction and by the fourteenth day counts on the fluid have averaged 250 leukocytes per cubic millimeter The reaction to ordinary spool cotton is similar However it has been noted that the cotton has less of a tendency to untwist Although perhaps not significant, the cell counts have averaged somewhat less In certain animals, these sutures have been allowed to remain for the period of one year with no apparent harm to the eye whatever The reaction to stain-

less steel wire can scarcely be measured. The vision of the eye is not impaired and cell counts made on the aqueous humor have averaged from five to ten leukocytes per cubic millimeter. However, when catgut is placed in the eye the aqueous humor becomes completely opaque in about ten days and the animal loses its vision completely. From outward appearances the anterior chamber is filled with pus. Cell counts of this fluid vary from 2 000 to 6 000 leukocytes per cubic millimeter. Cultures in every instance both in blood agar and beef broth have been negative.

In the group of animals in which sensitization to sheep serum has been carried out precipitin studies have demonstrated the precipitins in concentrations from 1 to 50 000. One tenth of a cubic centimeter of sheep serum subsequently introduced into the eye gives a marked inflammatory reaction characterized by edema and the coagulation of exudate in the chamber in a very few hours. Likewise segments of catgut placed in the eye of a sensitized animal produce a similar

severe reaction which has been interpreted as the Arthus phenomenon. The nonabsorbable sutures such as silkworm catgut do not produce this reaction in sensitized animals. Reaction to plain catgut is estimated to be twice as great as to chromic catgut. Likewise the Arthus phenomenon produced with plain catgut grossly is more severe than that from chromic catgut.

SUMMARY

Preliminary studies indicate that the anterior chamber of the eye is a suitable medium for observing the reaction of tissue to suture material. Sutures may be introduced with a minimum of trauma. Standard conditions are provided. Gross observation may be made continuously and quantitative cell counts may be made on the aqueous humor. A most striking difference in reaction is observed when nonabsorbable sutures are compared with catgut. Catgut apparently possesses antigenic propensities inasmuch as the Arthus phenomenon has been produced in animals sensitized to sheep serum.

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THE COOPERATION BETWEEN THE ARMY SERVICES OF EVACUATION AND HOSPITALIZATION*

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NEW YORK, N Y

AN ACTIVE, intelligent cooperation predicates a basic knowledge of the objects desired, the mechanism by which they are to be accomplished, the type, character and training of the personnel to be employed, and an estimate of the probable difficulties that will be encountered

It has been said, that the Army must change its tactics every ten years or suffer defeat. Since the last war, military tactics have undergone momentous changes. The present war has become one of mechanization and movement. The speed of the attack, the greater use of automatic weapons, combined with the moral and physical threats of an airplane attack, has greatly increased the difficulties of the Medical Department. Undoubtedly, the brunt of these difficulties will fall upon the collective, evacuation, and advance hospital services. Though the technic of triage, surgical management, and evacuation will necessarily be adapted to recent tactical concepts of mechanization and movement, the principles governing these matters will remain unchanged.

In the last war, the theater of military operations assumed the traditional fan-shaped pattern, the greater activity being in the periphery of the fan. In sharp contrast to this old pattern, the present military activities extend from the firing line to the home and beyond. In addition to this change of pattern, the tempo of all military activities has been speeded up. The attack is now designed to destroy the nation's vital resources before its full power can be mobilized, thus the defense of the home sector presents the Medical Department with a new problem. It is fair to assume that the Army staff has already worked out a master plan to meet such a situation. Have we as a body of surgeons given thought to such a possibility, have we considered how we can cooperate?

The first principle of military strategy is to assume the worst possible conditions, and then plan to meet them. It seems self-evident, that the only way to cover the medical situation arising in a total attack would be to

* Read before the American Surgical Association, White Sulphur Springs, W Va., April 29, 1941

mobilize the surgical and allied professions for the duration of the war. The acceptance of nationalization in such a crisis should become a duty and a privilege for us all.

An open slashing attack will have to be met by an equally mobile defense. It can be readily seen that the increased use of automatic weapons will lead to a more extended firing line, and every foot of extension will add to difficulties and dangers of the divisional collecting service. Some of these units will have to be furnished with protective armor, and the forward evacuation service will have to be provided with a motor equipment that can negotiate the roughest terrain.

In all probability, there will be an insufficient number of regular medical officers to fill all the executive surgical positions, and many of our profession will have to be assigned to such positions. If they are to function efficiently in the Army zone, they must have an elementary knowledge of what the military authorities expect of them.

Professional Peculiarities—All physicians, by the nature of their calling, are individualists. Much of our time and energy is devoted to making our patients follow orders. Subconsciously, we assume the attitude of command and without knowing it we become benevolent martinets. In all fairness to the rank and file of the profession, it must be confessed that the same tendency has been encountered in the professorial ranks and this often in a distinctly unphable form.

The active surgeon enters the service as a tried veteran in his life's work. Herein lies his advantage and his great military value. His surroundings have changed, but not his work. The civilian surgeon, anxious to give his best, must slough off the attitudes of the lone wolf and the commanding general, and cheerfully accept the vital military principle of coordinate control. The intelligent practice of this principle will unconsciously smooth out many rough spots in his adjustments to the new life. The mastery of this principle will automatically increase his surgical and military value, but above all it will enrich his own and his corps morale. Morale though intangible is the very soul of a successful army.

A study of what happened to our wounded in the Civil War shows in a most remarkable manner how history repeats itself. In the early years of the Civil War, the evacuation service was woefully inadequate in organization, equipment, and personnel. Very little improvement occurred until Letterman came on the scene. By 1864, the great value of a well-equipped evacuation service had been learned, and we find General Grant crossing the Rapidan with an Army of 73,000 men and 500 ambulances, that was one ambulance for every 146 men. If the First Army of the American Expeditionary Forces had anything like such a proportion, what a joy and a blessing it would have been.

The First Army Meuse-Argonne Offensive—The First Army contained more than 1,031,000 men. This is the largest single Army that the world has ever known. When the battle opened September 26, 1918, the Army

had 400 ambulances. Faced with such a shortage, it was vital that plans be devised to keep every wheel moving. In order to make the medical transportation liquid, all trucks, ambulances, motorcycles, *etc.*, were pooled and placed under the control of the ambulance director. The results obtained bore out General Sherman's famous dictum: "The more simple the principle, the more likelihood of determined action."

From a military standpoint, the care of the lightly wounded and their prompt return to their own combat units is a matter of paramount importance. Personnel trained under fire are of far greater value to a commanding general than raw replacements from the depot. General Sherman was so convinced of this, that he carried many of this type of wounded in his wagon trains in preference to hospitalizing them.

The experience of the last war taught that 20 to 25 per cent of the wounded brought to the evacuation hospitals could be returned to duty in less than a week, and an additional 20 to 30 per cent who pass through the evacuation hospital will be able to return to duty within ten to 12 days. The first group will consist of the exhausted, the pseudogassed, and the lightly wounded. This group should be promptly evacuated to the nearby Army convalescent hospital and from there to the Army replacement depot for forwarding to their combat units. The second group should be evacuated to the nearest general hospital in the zone of communications, with the express purpose of their prompt return to their combat units. The remaining wounded should be evacuated to the zone of the interior.

Evacuation Hospitals—The evacuation hospital is the pulsating heart of the evacuation system, and it is the direct responsibility of the surgical director and the surgical teams to see that a bottleneck does not occur. If you have ever had the misfortune to see one of these bottlenecks, you will never forget it. They did occur.

The evacuation hospital service must plan for the prompt clearing of the incoming ambulances with the exchange of splints, stretchers, blankets, *etc.*, and be prepared in a like manner for an outgoing evacuation. Great delay was experienced at some of the Army hospitals due to the poor provisions made for this essential service. The ambulance drivers were quick to sum up the efficiency of the hospitals in terms that were endearing and otherwise. They alluded to the hospitals as the outfits of Longshanks, Fats, Slat, Valentino, and Weasel Face. Perhaps some of the members can identify one of our honored Fellows, who bore the endearing title of Longshanks.

The Handling of the Lightly Wounded in the Army Hospitals—The evacuation service of the Army felt keenly that entirely too many unoperated cases were evacuated. In the first phase of the offensive 11,370 men, supposedly simple cases, were potential sources of trouble, through the possibility of their wounds becoming infected. Reports from the rear soon showed that our fears were well-grounded.

This poor operative output was due to the inexperience of many of the teams in this field of work, and to the inherent difficulty of making profes-

sional men think of the wound in terms of military value, rather than in terms of professional interest. In the majority of evacuation hospitals, the organization and facilities for handling this important class of wounded were very defective. The chief surgeon of the Army, realizing the urgency of the situation, instituted radical changes in the handling of the lightly wounded. The lightly wounded were triaged, assigned special roentgen ray equipment, special operating rooms, special surgical, splint, and anesthesia teams. Experienced surgeons of good judgment who thought and acted quickly were selected. The slow careful operators were assigned to other types of cases. The newer anesthetics, well-selected, will be a very important factor in facilitating this important work.

The Lightly Wounded Production Line—This line was operated on the system of three to four tables to a surgeon. Its practical value soon became apparent. In the second phase of the offensive, only 293 unoperated cases were evacuated. The perfection of this method was due to Lt. Colonel George Davis, of Chicago, and his able assistant, the late Major Sherbondy. Some of the teams cleared 80 to 100 and more cases in their shifts. Colonel William Darrach was energetic in spreading the gospel of this method and in this he was ably supported by Lt. Colonel Marshal Clinton. The surgical staff of the First Army can justly feel proud of the result obtained. It has not been matched in our Army, or in any of the Armies of our Allies.

Every evacuation hospital should be simply but adequately equipped and its personnel thoroughly trained in the functioning of the lightly wounded production line. The first requisite is an ample floor space. Dinky little trailer and automotive operating rooms are next to useless, and not worth the gas they use. If suitable space is not obtainable in permanent buildings, experience has shown that there is nothing better than well-arranged tentage, in fact it is ideal for the smooth functioning of the lightly wounded production line. The roentgen ray and sterilization equipment can be of the automotive or portable types, or a combination of both. In this way, the production line can be geared to meet any situation. Simplicity, direct action, and coordination are the driving power of the line.

Liaison—One of the most difficult ambulance problems in the big offensive is to insure an even distribution of the wounded to the Army hospitals. Its solution is only possible when there is the closest active coordination between the director of the corps ambulances, the director of the Army ambulances, and the evacuating officer of the Army hospitals. Fortunately, in the First Army, this relation was intimate. The technical working from the side of the Army was facilitated, as one individual was the consultant in surgery for the First Army, and in addition he held the interlocking positions of director of the evacuation of the wounded and the director of the Army ambulances.

The sound judgment, the tireless energy, and the splendid whole-hearted spirit of coordination displayed by the divisional and corps ambulance directors made the seemingly impossible, possible. Certain definite hospitals were

assigned by the chief surgeon for the wounded of each corps. In the main, this was a wise provision, but there were times when the Army found it necessary to make a rapid readjustment to meet the exigencies of the moment.

All deficiencies in divisional ambulances were filled up through lending sections to the corps, and in addition a section from the Army reserve was attached to each corps. They took care of its local emergencies. The main Army ambulance reserves were parked in echelon. The first, one hour from the line, the second, two hours from the line. In this way, the reserves could be readily shifted from one corps to another as the circumstances required.

Secondary Duties of the Ambulance Service—A maintenance of a motor courier service for liaison purposes, the rationing of the French trains, daily forwarding of medical supplies, *etc*, were performed by the ambulances returning to the front. Some of the evacuation hospitals and special hospitals entered the Army without motor transport. These had to be moved and serviced with medical supplies, rations, fuel *etc*, and in a few cases with water, the transportation of surgical teams, nurses, and medical personnel, baggage, *etc*. Forty-three hundred passengers were carried during the offensive.

Road Control in Reference to the Evacuation of the Wounded—In the Army zone, certain roads were assigned to the division, the corps, and the Army. The type of transportation and its direction were under the immediate control of the military police, and their word was law. Daily reports of the roads to be used, their condition, danger zones and maps, indicating all changes in position and direction, were furnished the ambulance director (See "The Report for the Evacuation of Wounded in the Meuse-Argonne Offensive").

Directional Signs for the Evacuation Hospitals and Their Importance—The name of the hospital with a directional arrow should be displayed in large plain letters on a sign of adequate size. These signs should be placed at key points along the corps and Army roads. The signs should be illuminated at night, so that the ambulance driver will know at a glance where he must go. Driving without lights on a dark rainy night, along unknown roads, is a difficult and uncertain task. In the early phases of the offensive, until the road control was perfected, the lost and wandering ambulance with its load of wounded was demoralizing.

The Bedeviling of the Ambulance Drivers and the Mixing Up of the Corps Wounded—In the opening days of the offensive, a few overenthusiastic commanders of evacuation hospitals, without authority, placed road signs directing the ambulance drivers to their hospitals. Unfortunately, they did not confine their activities to their own corps area, nor did they consult the military police, in fact they successfully succeeded in throwing a monkey wrench into the evacuating system which led to the overcrowding of certain hospitals. The bedeviled ambulance drivers were like lost souls, trying to find a resting place for the weary wounded. Fortunately, the mix-up did not

last long, the military police discovered the trouble, and promptly ripped down every unauthorized sign

Consultants — It is imperative that the consulting service should prepare definite plans well in advance of any offensive. They should weigh carefully the effect of their policies on the service of evacuation and hospitalization. It is extremely difficult for the civil surgeon, without military experience, to grasp how closely these two services are integrated and what a confusion can be caused by last-minute changes. The surgeons with a few alert medical men grasped this principle and put it to practice, while other medical consultants preferred to sleep and dream. Some of them are still sleeping.

The Army Consultant — The Army consultant must be more than an individual diagnostician and his vision must not be dimmed by the eyeglasses of specialism. He should be a surgeon of from 40 to 45 years and no older. Men of more mature years with active minds and vision should be attached to the zones behind the Army as general consultants. Here their talents will be of greater value to the wounded. A knowledge of the rudimentary military principles will enhance value of all consultants.

In the First Army, the consultants endeavored to bring into the office of the chief surgeon information that would be of value to him in the improvement of the professional care of the wounded and, at the same time, to furnish him with the detailed information regarding the proper care of the patient in the divisional and corps areas.

The reports showed that there were considerable differences in the evacuation time of the divisions, that is, the time that elapsed between the wounding of the patient and his reception in the Army hospitals. The reports from the Army hospitals showed that the best results in cutting down infection and saving life were obtained by those divisions which, in spite of all difficulties, managed to get their cases back in good time. The marked difference between some of the divisions was due to the fact that there was a tendency in certain of them to hold the case for operation. The condition of the roads failed to explain the marked discrepancy between the divisions. There were certain divisions which from the moment they entered the Army area till they left, managed to get their cases back on time.

Special Surgical Hospitals — Experience had taught the First Army that it was impracticable, wasteful, and harmful to attempt to triage selected wounded for individual specialty hospitals. In order to function efficiently, these hospitals had to be provided with a special evacuation service. The Army evacuation service, faced with an acute ambulance shortage, felt that such a waste of ambulances was not justified. To still the persistence of a well-meaning consultant, who desired the establishment of a specialty hospital a tentative trial was undertaken by the chief surgeon of the Army. It proved to be a miserable failure. In the zone of communication and the interior, the separate specialty hospital is a very valuable asset, but in the combat zone, it is simpler and more practicable to install special operating teams in the evacuation hospitals.

The Hospitalization of the Nontransportable Wounded—Experience showed that large hospitals were not necessary. A small hospital of about 50 beds and two surgical teams is all that is required provided the hospital is strictly limited to this class of wounded. The hospital should be located close to the divisional triage center so that the direct lettering of the wounded is possible.

In the larger hospital, there was a distinct tendency by ambitious surgical teams to fill the empty beds with operative cases. In fact, some of the units became baby evacuation hospitals and the clearing of these hospitals added another unnecessary burden to the overwrought motor transport of the front.

The present surgical hospital has 400 beds. They are assigned one per front-line division and they are placed in immediate support of the divisional clearing station. As they are not motorized, the Army furnishes the transport. In the last war, this high-sounding phrase was heard not infrequently by the evacuation service. It was a headache and meant "George, you do it." And George had "to do it."

The Peddling of the Wounded—No well-organized evacuation hospital should ever refuse admittance to the wounded. To force the ambulance driver to peddle the innocent wounded is a detestable practice. We consider it the lowest form of the abuse of power.

CONCLUSIONS

(1) The basic principles of all military surgery is debridement. Chemotherapy and immobilization in plaster are adjuncts. The more extended use of the roentgen ray and the employment of the newer anesthetics should greatly extend the usefulness of the military surgeon. (2) An efficient evacuation and hospitalization is the backbone of all treatment, without it, surgery is hamstrung. (3) On the proper triage, adequate motor transport, and the will to see it through rests the success of the evacuation of the wounded. Undoubtedly, a well-developed airplane transportation will become a very valuable asset. (4) The evacuation of the wounded will always be a difficult and complicated task of great responsibility. As surgeons, it should be our duty and our pride to see that the stream of wounded flows steadily onward without a check. (5) As individuals, we are apt to be dogmatic, and it is difficult for us to accept the principle of coordinate control.

I am convinced that we all can profit by Oliver Cromwell's admonition "My brethren by the Bowels of Christ I beseech you, bethink you that you may be mistaken."

DISCUSSION—DR MORRIS K. SMITH (New York, N. Y.) Doctor Lyle speaks with particular authority on the subject about which he has addressed us. After holding various posts of increasing responsibility in the last war, he was, during the Meuse-Argonne offensive, director of ambulances and evacuation of the wounded and chief consulting surgeon of the First Army. In this campaign 126,000 sick and wounded were evacuated to the railhead hospitals. I would urge that those of you who may be anticipating service in the front areas, should we enter this war, study thoughtfully what he has to say.

It appears inevitable that campaigns characterized by the increased mechanization

and mobility that has so far marked the present conflict should offer new and more difficult problems in the evacuation and hospitalization of the wounded. What little I have been able to find in the literature on the subject emphasizes an increased need of coordination in the medical services and a greater supply of ambulances. The underlying principles of efficient evacuation and prompt and competent handling of the wounded man remain the same, however. To these ends, Doctor Lyle's experience affords valuable lessons.

The civilian surgeon who finds himself in front area field service in war has to realize that evacuation of sick and wounded rather than treatment is his primary responsibility. In times of activity its smooth functioning is dependent on well-coordinated efforts from regimental medical service down the line. It is important that the supply of ambulances be adequate and efficiently utilized.

At the evacuation hospitals, a blockade can easily arise. Doctor Lyle stresses particularly the importance of separate teams, with their own assignment of roentgen ray equipment and operating units, for the handling of the lightly wounded. This facilitates prompt treatment and rapid turnover for this large group who are, as he points out, from the Army standpoint the most important, because of the possibility of their early return to duty. To this end, they should be evacuated to nearby convalescent and replacement areas rather than to distant hospital centers.

Doctor Lyle has found special surgical hospitals in the front areas impracticable. He also feels that front area units for nontransportable wounded should be small.

In the hospitals, well away from the combat area, where continued treatment of the sick and wounded is planned the erstwhile civilian surgeon will find new problems which will challenge his professional skill, because the types of injury will be different from those to which he is accustomed at home. But, none the less, he will be in an hospital environment, his familiar workshop. In the front areas, he must adjust himself to greater changes. There the problem is collecting, sorting out, and sending on the wounded and sick. In the evacuation hospitals, the surgeon will be doing primary surgical treatment but he must cope with the reception, handling, and evacuation of large numbers of patients in the shortest possible time. Careful planning and disciplined performance of duties are essential.

DR WILLIAM DARRACH (New York, N. Y.) I should like to speak on the treatment of compound fractures but, unfortunately I have another thought which I want to emphasize, and that is that if we are going to live up to the function of the Medical Department we have to be hard-boiled. The function of the Medical Department is to maintain the fighting strength. If we are going to live up to that, we should concentrate our major efforts on those wounded who can be and may be returned to the fighting forces.

That means that all the special groups, the highly trained and efficient compound fracture surgeons, the maxillary, the head surgeons, the chest surgeons, the belly surgeons, belong not to the main function of the Medical Department, but to their secondary purpose of humanitarian care of those who are severely wounded and who never will go back. We cannot omit handling those people, because part of our duty is to maintain the morale. If we were strictly hard-boiled, we would pay attention only to the lightly wounded. We must pay some attention to the severely wounded, but they should be of secondary importance. Therefore, I think that if the idea that was carried out in a small way, but sufficiently to prove that it can be done, by Joe Davis and Sherbondy and one or two other attempts, whereby the lightly wounded can be handled at the rate of five or six an hour, instead of one case per hour, as most of us were doing on the heavier cases, were really carried out we would find that our Medical Corps work was more efficiently done, and we would restore more men to the fighting forces.

I had one brief experience of almost eight hours of doing this work with the British Clearing Station No. 47. In taking these lightly wounded cases, we could do about four or five an hour there, but the next day the commanding officer came around and said, "I am sorry, but this is not done in the British Army," so we stopped.

Again, in the first corps, there was an excellent plan made for putting an Evacuation Hospital up fairly close, where the lightly wounded could be handled at this rate of rapid production and kept in that area and sent back, but unfortunately for that scheme Armistice came along and spoiled it. I would like to see that scheme put into effect, and that the major function of the Medical Department be recognized as restoring the fighting forces.

THE DIAGNOSIS AND TREATMENT OF CARDIAC TRAUMA*

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ALTHOUGH the suture of heart wounds is classed as an attainment of modern surgery, a knowledge of their fatal outcome, if untreated, has been recognized from the earliest times. For the student interested in the history of cardiac surgery, an interesting point of departure would be the *Iliad* and the *Odyssey*, for the Homeric stories abound with reference to cardiac wounds. Hippocrates¹ realized their fatal nature, as did Pare,² who described them, but made no suggestions regarding their treatment.

Boerhaave³ stated that all wounds of the heart were mortal. Hunter made no mention of the subject, and John Bell,⁴ in his "Discourses on the Nature and Cure of Wounds," devoted only two paragraphs to the subject, although he recognized the signs and symptoms of the condition and cited two patients who lived several hours, who might well have been saved by operation. He thus discussed the subject: "There is so little to be done . . . and the signs and consequences are so clear, that it were a waste of time to speak longer of wounds of the heart." Billroth,⁵ who dominated the surgery of his day, wrote (in 1875) "Paracentesis of the pericardium is an operation which, in my opinion, approaches very closely to that kind of intervention which some surgeons would term a prostitution of the surgical art and other madness." He did add, prophetically, "Perhaps another generation will think otherwise about it." As late as 1896, Stephen Paget⁶ wrote "The surgery of the heart has probably reached the limits set by nature to all surgery, no new method and no new discovery can overcome the natural difficulties that attend a wound of the heart."

Two figures stand out because of their disagreement with these pessimistic pronouncements, Morgagni⁷ who, in 1761, showed that blood in the pericardium compressed the heart and embarrassed its movements, and Baron Larrey⁸ (Napoleon's great surgeon) who decompressed a wounded heart by drainage, and who demonstrated by experiments on dogs that these injuries were not necessarily fatal.

Modern surgery of the central circulatory system began with Roberts⁹ (1881), who suggested that wounds of the heart be sutured. Black¹⁰ (1882) successfully sutured the hearts of rabbits, but de Vecchio¹¹ (1895) deserves greater credit for demonstrating to the Eleventh International Medical Congress, at Rome, the healed wound in a dog's heart. Within a year the human heart was sutured by Cappelen¹² (September, 1895), by Farina¹³ (March 1896), and Rehn¹⁴ (September 1896). Rehn's patient survived. By 1909,

* Delivered on the occasion of the receipt of the Matas Vascular Surgery Award, Tulane University, New Orleans, La., November 14, 1940.

Peck¹⁵ was able to collect 161 cases treated surgically, with a mortality of 63 per cent. Pool¹⁶ (1912) added 79 cases, with a mortality of 49 per cent, Smith¹⁷ (1923) collected 25 cases, with a mortality of 36 per cent, and Bigger¹⁹ (1932-1933) added 70 instances, with a mortality of approximately 30 per cent.

The percentage of reported recoveries is unquestionably too high, because of the fact that many single, favorable cases have been reported, whereas those ending fatally are not so likely to be recorded. At any rate, the percentage of recoveries is at the present time at least 50 per cent, whereas only 10 per cent of the untreated cases reported by Fischer²⁰ (1868) recovered.

Incidence—Wounds of the heart are relatively rare. In southern hospitals they comprise about 0.1 of 1 per cent of patients. At Emory University, 2 per cent of the penetrating wounds of the chest injured the heart. Considering its size and exposed position, it is surprising that it is not more frequently injured. If those patients were considered who die of homicide, suicide, and accident, but never reach the operating room or the autopsy table, it is probable that the percentage would be much higher. Moreover, the diagnosis is frequently overlooked, and patients may die without surgical intervention who might otherwise have been saved had early diagnosis been made and prompt surgical intervention undertaken. That cardiac wounds are more frequent than is generally supposed is evidenced by the ever-increasing number that are reported. At Emory University, the number of patients treated for wounds of the heart has increased steadily each year since 1930. This is merely another evidence of a better ability to diagnose the condition, since the number of chest injuries has decreased.

Mode of Injury—For the most part, penetrating wounds of the heart are produced with homicidal or suicidal intent, and, therefore, knives, ice-picks, and pistols are the most frequent weapons with which the injury is inflicted. In addition, the heart may be wounded in crushing injuries or by its accidental penetration by glass and splinters as a result of automobile accidents. Aside from penetrating wounds, contusions of the heart, fatal or nonfatal, may occur. In any event, early diagnosis and treatment is necessary since delay is rapidly fatal.

Cardiac Tamponade—Rapid changes in pressure relationships, particularly within the pericardium, affect the filling and emptying of the heart and, if unrelieved, will quickly bring about a standstill of the cardiac mechanism. The diagnosis of acute cardiac compression, the removal of its cause, and the prevention of its recurrence, is the basis for the treatment of cardiac injuries.

Normally, the intrapericardial pressure is less than that of the atmosphere, and the pressure in the intrathoracic portions of the venae cavae is probably negative. With the rapid accumulation of fluid in the pericardium, as from pus or blood, the venous pressure rises, and after it reaches a height sufficient to overcome the increased intrapericardial resistance, blood enters the heart, and the circulation continues. Normally, the venous pressure ranges between

75 and 120 Mm of water. In rapidly increasing accumulations of fluid, the pericardium cannot distend sufficiently nor can the venous pressure rise to such a level as to allow the filling of the heart for any length of time. However, I have noted a venous pressure as high as 400 Mm of water in acute compression of the heart, and have seen this pressure maintained for as long as 30 minutes without a fatal result. Where the tamponade of the heart is gradually produced (serous effusion), the pericardium is slowly distended and a high venous pressure will maintain the circulation for days.

Acute tamponade leads to cerebral anemia, for the heart can no longer fill. Release of tamponade is, therefore, a matter of first importance, and demands immediate treatment. The symptoms are a low or unobtainable arterial pressure, a high or rising venous pressure, and a quiet heart. The pulse is weak or absent, and the veins, particularly those of the neck, are prominent and struffed. Because of the venous stasis there is a marked cyanosis of the lips and tongue.

Diagnosis—Because of its position in relation to the anterior chest wall, a wound of the right ventricle is more frequent, but wounds of all four chambers as well as those of the intrapericardial portions of the great vessels may be encountered. The exact location of the wound can only be surmised before operation, since symptoms from bleeding or tamponade will be the same, regardless of the location. Death may occur from rapid loss of blood either into the chest or to the outside, but death is more likely to occur as a result of tamponade.

The history is usually characteristic. There is freedom from symptoms for several minutes after the injury, followed by exhaustion, and then loss of consciousness. Either stupor or wild delirium may follow. Patients have been known to walk several blocks or to continue fighting for as long as five minutes after a wound of the heart. Bleeding is profuse at first, but soon stops. This train of symptoms is due to a rapidly increasing tamponade. When the heart is wounded, it bleeds freely to the outside and usually into the pleural cavity as well. At the same time, some blood collects in the pericardium and when 100 to 200 cc have so collected, the heart becomes compressed. Contractions become weak, and bleeding to the outside stops. With the rise in intrapericardial pressure, the venae cavae can no longer convey normal quantities of blood to the heart, and cerebral anemia, as evidenced by unconsciousness, results.

The position and direction of the wound may aid in diagnosis, but the course of a bullet, or even a knife thrust, is notoriously misleading, although those near the left of the sternum from the second to the fifth interspaces are most apt to injure the heart.

Accurate diagnosis, above all, will depend to a large extent upon the Resident Staff, who must be trained to be ever on the alert not only to recognize symptoms of cardiac trauma, but to suspect every chest injury as a potential heart wound. All too frequently, wounds considered inconsequential

may later prove to be fatal. This is particularly true in a case where an ice-pick has caused the wound.

The skin is usually cold and moist, and because of the venous congestion there is a cyanosis of the lips and tongue. The heart sounds are weak, often irregular, and the pulse is weak or imperceptible.

The arterial pressure is lowered, even unobtainable, and the venous pressure is raised as evidenced by prominent, strutted veins, particularly those of the neck. By direct measurement, this pressure is frequently above 200 Mm. of water, and a rise to 300 Mm. of water is not unusual. Such a pressure is consistent with life if not maintained for too long a period. Venous pressure readings should be obtained by the direct method of inserting a needle into a basilic vein and noting on an attached manometer the height at which a column of physiologic salt solution is maintained. The patient's body should be horizontal, and the vein should be on a level with the heart.

Roentgenograms are of no value, since death may occur from an amount of blood in the pericardial sac too small to cause a noticeable change in the size and contour of the heart shadow. Fluoroscopic examination, as shown by Bigger¹⁹ is of great value, since the normal pulsations are prevented by a small accumulation of blood in the pericardial sac. Of all the diagnostic aids, this is the most accurate in proving or disproving one's suspicions of cardiac tamponade. It had best be undertaken with the portable fluoroscope, for with this unit the patient need only be turned on his side for examination.

To summarize

(1) There is usually a history of freedom from symptoms for several minutes after the wound has been received, followed by rapid collapse and unconsciousness.

(2) Heart sounds are weak, as is the pulse.

(3) The arterial pressure is lowered.

(4) The venous pressure is raised.

(5) Fluoroscopic examination shows a quiet heart.

Operation should be carried out as soon as the diagnosis is established. To hasten and facilitate this, all necessary instruments should be kept ready in a separate container. Since infection of the pericardium and pleura is a frequent complication, meticulous care in preparation and technic should not be sacrificed for speed and haste. While preparations are being made, sufficient morphine should be administered to insure rest and quiet. The head should be lowered and the body kept warm. Theoretically, intravenous infusions are of little value so long as tamponade is present, but where excessive hemorrhage has occurred, it is indicated. The administration of a 6 per cent solution of acacia may be life-saving, and autotransfusion of the blood removed during the operation should be citrated and administered when possible. Blood transfusion should be undertaken as soon as possible after the release of the tamponade. For this purpose the "blood bank" is an invaluable aid.

Anesthesia—Inhalation anesthesia is preferable to local anesthesia for

several reasons. The pleura may have been opened by the wound, or may be accidentally opened during the operation, and nitrous oxide and oxygen under positive pressure is necessary for the inflation of the lung. The difficulties of heart suture require that the patient be quiet, but these patients are usually wildly excited or are apt to become so with release of the tamponade, and unless completely anesthetized their struggles may interfere with the operation at a most inopportune time.

Suture of the Heart—The incision should be so planned as to give the best exposure with the least trauma. It must also be made with some consideration as to the position of the external wound. Although the pleura is usually injured when the heart is wounded, further tearing of this membrane should be avoided if possible, for it adds greatly to the shock of the patient. For that reason dissection of the pleura from the pericardium is best begun in the fourth or fifth left interspace because of its lateral reflection at that point. It is this reflection to the left which leaves the pericardium uncovered by pleura at that point and so facilitates an extrapleural approach to the pericardium. It is of importance to remember that the costomediastinal lines of pleural reflection vary greatly, thus, either the left or right pleura may cross the middle of the sternum (Fig. 1). In a composite study of anterior pleural margins, Vosnitch was able to outline a small triangle of safety where the pericardium was uncovered by pleura. This lies behind the sixth left costal cartilage and sixth interspace (Fig. 2).

Unless the skin wound is well to the right of the sternum, the approach to the heart should always be made on the left, and the incision should be so planned that it can be readily enlarged if the heart wound is not easily located. With these factors in mind, experience has shown that a long transverse incision extending well across the sternum gives the best exposure (Figs. 3 and 4). By this approach one or two ribs can be removed, and, if necessary, the adjacent costal cartilages cut and a portion of the sternum removed. The pectoralis major muscle is separated in the direction of its fibers and can easily be retracted from the surface of three ribs. Dissection should begin well out on the rib, which can be easily lifted from its periosteal bed and cut without injuring the pleura. By lifting the rib, the cartilage can then be removed with less danger of injury to the pleura than if the cartilaginous portion is removed first. The internal mammary vessels are ligated and cut, the triangularis muscle is divided, and the pleura is displaced outward by careful gauze and finger dissection.

A second incision, and one giving excellent exposure, consists of turning a musculocutaneous flap laterally and removing two or more costal cartilages and ribs (Fig. 5). It requires more time to open and close the chest wall and is more likely to induce shock.

The incision should be planned to secure the best exposure in the quickest time and with the least shock. The median sternotomy (Duval-Barasty) (Fig. 6) gives excellent exposure to all the heart and the great vessels, but splitting the sternum requires a great deal of time, as does the closure of

the wound, and is productive of shock. It is mentioned only to condemn it, since in cases of severe hemorrhage or increasing tamponade the patient would not likely survive such a procedure.

The intercostochondral thoracotomy (Spangano) offers a rapid approach to the heart but not a particularly good exposure. It can be enlarged by cutting or removing the cartilages above and below the incision and by removing a portion of the sternum.

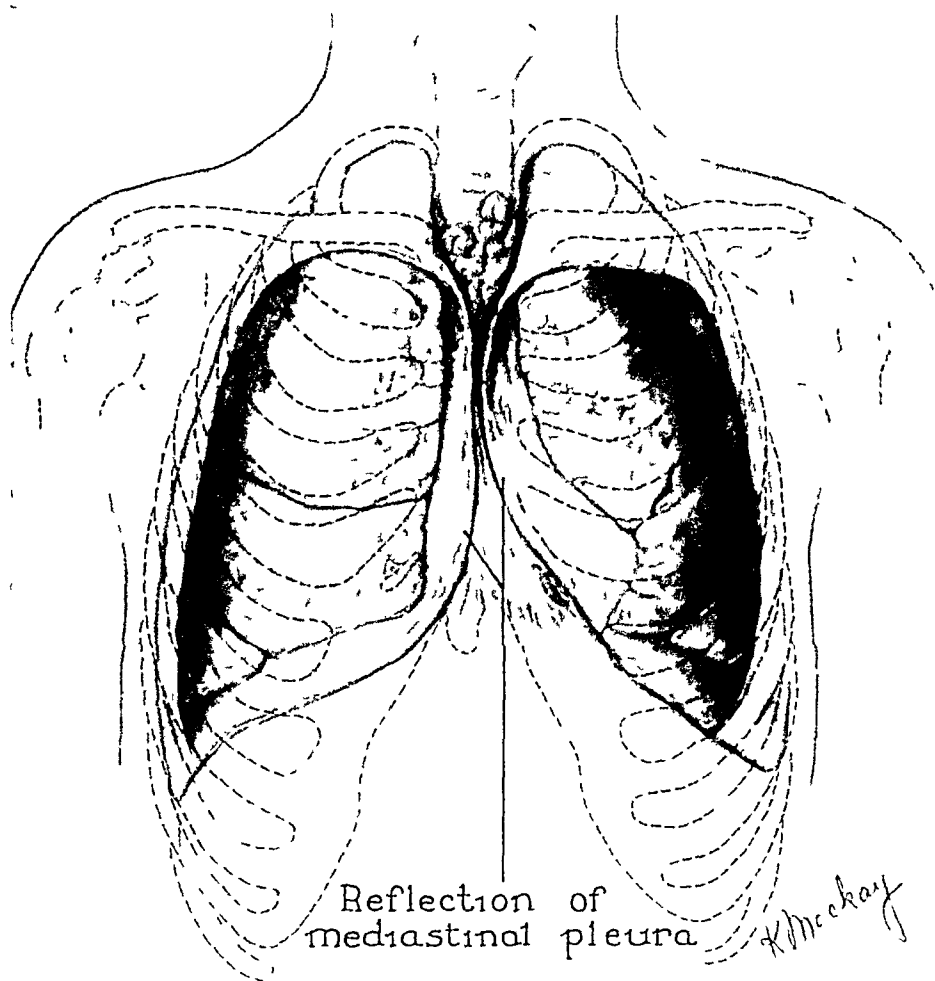


FIG. 1.—The usual anatomic relations in the anterior mediastinum.

The pericardium will be tense, bulging, and blue, and its pulsations will be weak and imperceptible. If the wound in the pericardium is seen, it should be enlarged, or, if not readily found, it is opened between stay-sutures of silk (Fig. 7). Occasionally, the heart wound can be located before the blood and clots are removed and before the heart starts bleeding profusely. If it is not immediately seen, the blood and clots are removed by suction. When the intrapericardial pressure is relieved, the bleeding becomes marked,

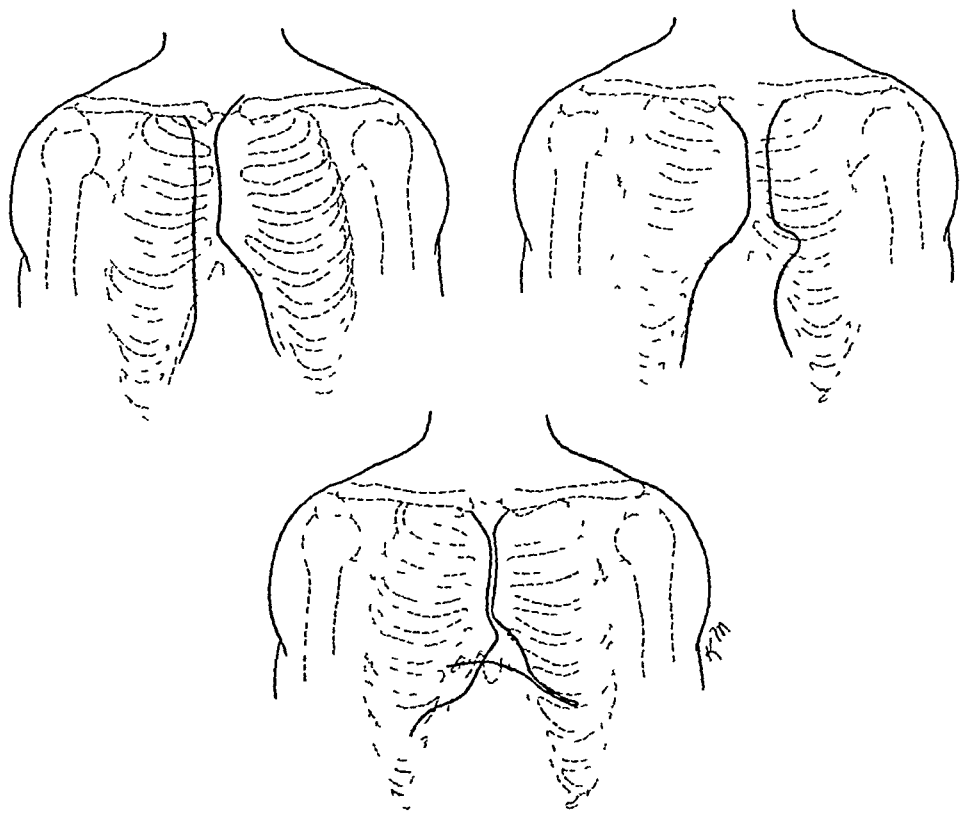


FIG 2—Diagrammatic representation of the lines of pleural reflection. Lower figure shows the triangle of safety (Matis)

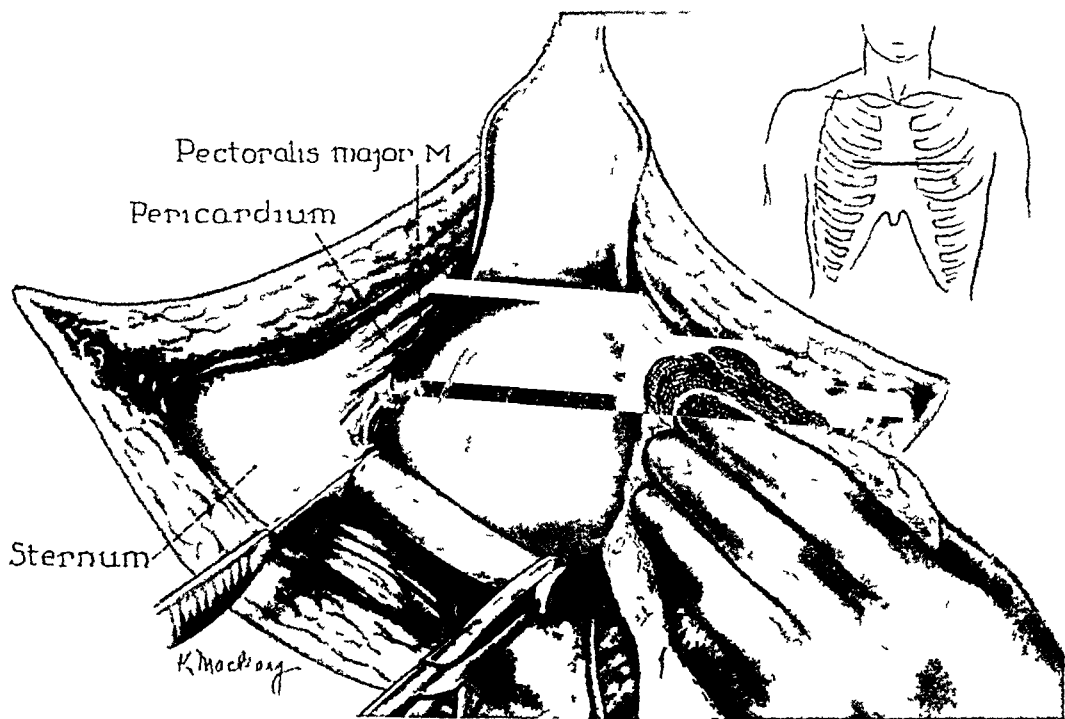


FIG 3—Showing the transverse incision, the removal of two ribs, and exposure of the pericardium

as the contractions of the heart increase in force. When the wound is located, and it is most often found in the right ventricle, its closure is facilitated by placing the left index finger over it. In this way the bleeding will be impeded sufficiently to allow the passage of a suture directly under the finger. This is left untied for the moment and is held in the left hand for traction and hemostasis while other sutures are placed and tied. They should pass well into the substance of the muscle, but not into the chamber of the heart. Fine black silk on curved calyx-eye needles is the material of choice. Heart muscle is extremely friable, and for this reason, the finger should not be placed in the wound, and sutures should be tied with only enough tension to approximate the edges (Fig 8).

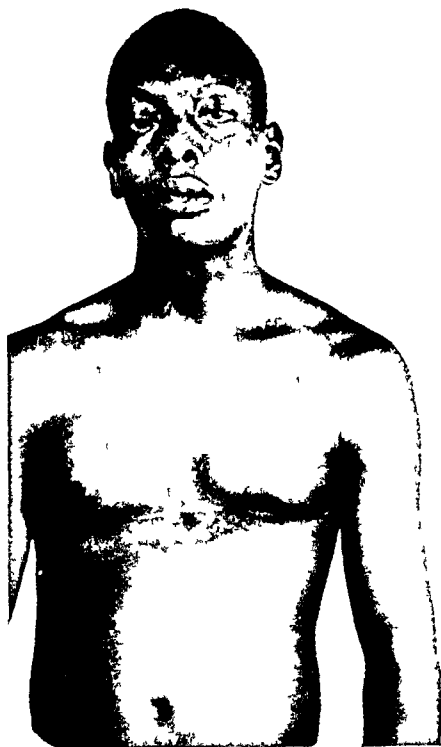


FIG. 4.—Patient showing a healed transverse incision.

Should the wound be behind the sternum or on the posterior surface of the heart, a stay-suture passed through the apex, as advocated by Ballance and by Beck, may be of great value, for by this means the heart may be rotated into such a position that the wound may be more easily sutured (Fig 9).

Wounds in Special Positions—Wounds of the auricle bleed with great rapidity and are more difficult to close because of the thinness and friability of the musculature in this location. Occasionally, a clamp, such as that used by Tiendelenburg in closing the pulmonary artery may be applied directly over the wound and the hemorrhage controlled until sutures can be taken (Fig 10). If possible, sutures should not be carried into the chamber of the auricle because of the danger of an intra-auricular clot. Intra-pericardial wounds of the great vessels will produce the same symptoms of tamponade as wounds in the heart muscle itself. They, too, are difficult to close because of the thinness of the structures. If the wound is in the pulmonary artery or aorta, the hemorrhage may be checked by passing the Tiendelenburg probe behind them and thus impeding the flow of blood until the sutures can be placed (Fig 10). Injuries to the coronary vessels may require ligature but are not necessarily fatal. I have found it necessary to ligate a major coronary vessel in three instances. All three of these patients survived, showing that this is not necessarily fatal. Electrocardiographic tracings in these patients show the typical findings of myocardial infarction. Where bleeding is so profuse that the wound cannot be located, it is sometimes necessary to resort to the procedure of Sauerbruch. In this, the venae cavae

are clamped and the heart is opened by a transverse incision in the septum between the two ventricles. This procedure is rarely necessary, but it is a last resort. In the case of a wound in the left ventricle, the same principles apply as in the case of the right ventricle. The wound should be located, and the left index finger should be placed over it to facilitate the passage of a suture. The suture should be tied with only enough tension to approximate the edges. The same principles apply to wounds in the left atrium and the great vessels. The wound should be located, and the left index finger should be placed over it to facilitate the passage of a suture. The suture should be tied with only enough tension to approximate the edges. The same principles apply to wounds in the right atrium and the great vessels. The wound should be located, and the left index finger should be placed over it to facilitate the passage of a suture. The suture should be tied with only enough tension to approximate the edges.

are grasped between the middle and ring fingers of the left hand, and the first finger and thumb are left free to compress the cardiac muscle (Figs 11 and 12). Needless to say, such a compression can be carried out for only a few minutes. During the course of any cardiac operation the heart may fibrillate or even stop beating, especially when traction is applied, or direct compression or kinking of the great vessels is employed. Should this occur

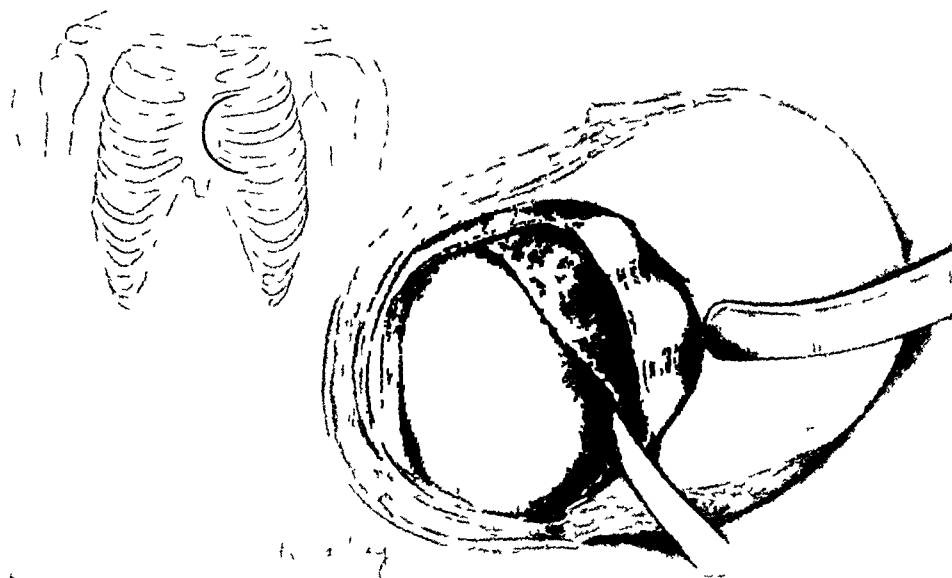


Fig. 5—The approach to the pericardium through the musculocutaneous flap

the operation should be momentarily stopped until normal contractions are resumed. The injection of one cubic centimeter of 1:1,000 solution of adrenalin directly into the heart muscle is frequently of value in restoring contractions. Gentle massage by pressure between the index finger and thumb will likewise often restore the heart beat.

After suture and control of the hemorrhage, the pericardial cavity is cleansed by suction and flushing with salt solution. The pericardium is loosely closed with interrupted sutures of silk, leaving sufficient space between the sutures for the escape of any fluid which may accumulate. Occasionally, the heart dilates to such an extent that complete closure of the pericardium is impossible. The muscle, fascia, and skin are then closed without drainage.

After operation the patient should be placed in an oxygen tent. Fowler's position will usually facilitate breathing. Morphine should be administered in sufficient amounts to insure rest and quiet.

Since the pleura and lung are often injured at the time of the heart injury, hemopneumothorax is frequently present. If its extent is such as to cause embarrassment of respiration, aspiration of the chest should be done, but in the absence of symptoms it is better to allow absorption of the air and blood.

Prognosis—Immediate prognosis depends largely on the interval between

the injury and the operation. Delay may cause death from hemorrhage or tamponade or both. It likewise depends upon the character and extent of the injury, a bullet usually causes two wounds, with greater hemorrhage and tissue loss, and is rapidly fatal. Postoperative prognosis is largely dependent upon infection. Purulent pericarditis is apt to follow these wounds, which are necessarily contaminated and which may carry with them bits of clothing or other foreign material. Pneumonia resulting from lung injury, or as a part of the generalized infection, may likewise follow.

Thirty-eight patients with heart wounds have been operated upon by me or my Resident Staff (Fig. 13). Of these, 22 recovered and none of them have any residual symptoms referable to the injury. All wounds were pro-

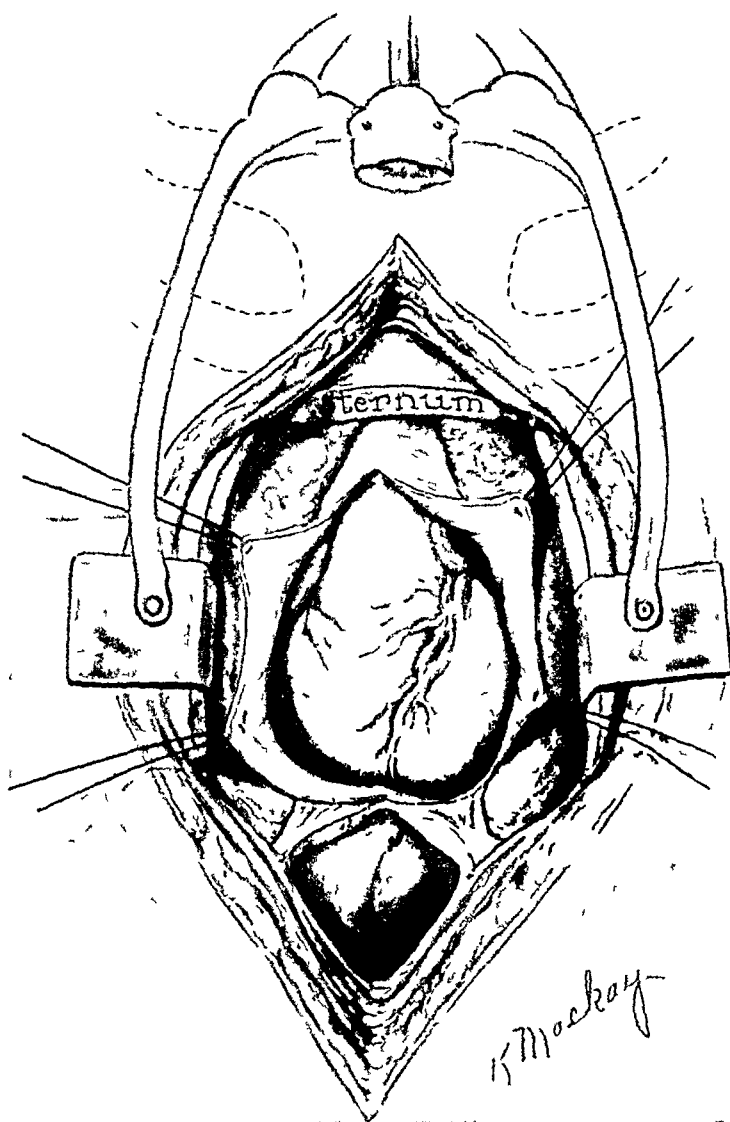


FIG. 6—The Duval-Burke's median sternotomy (after Cutler)

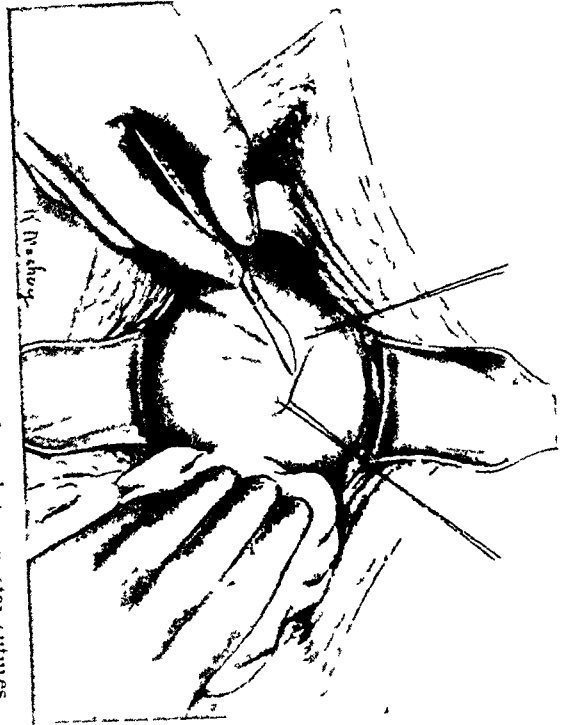


Fig 7—The opening of the pericardium between stay sutures

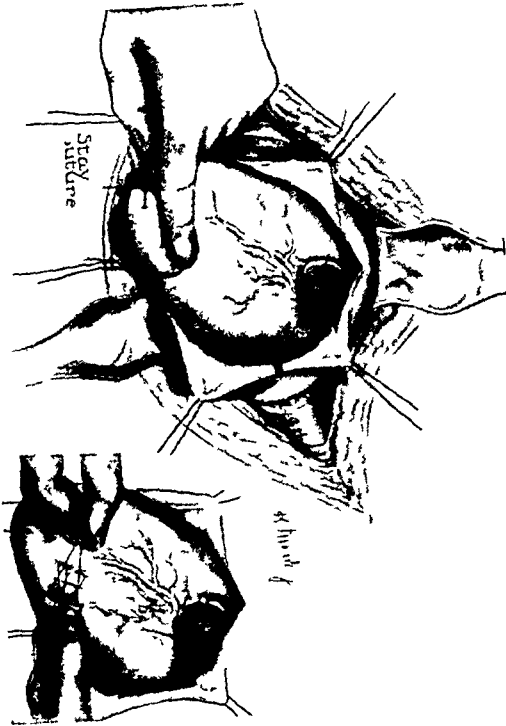


Fig 9—The use of the stay suture in rotating the heart into position for suture (after Beck)



Fig 8—Method of controlling hemorrhage while suture is passed under finger

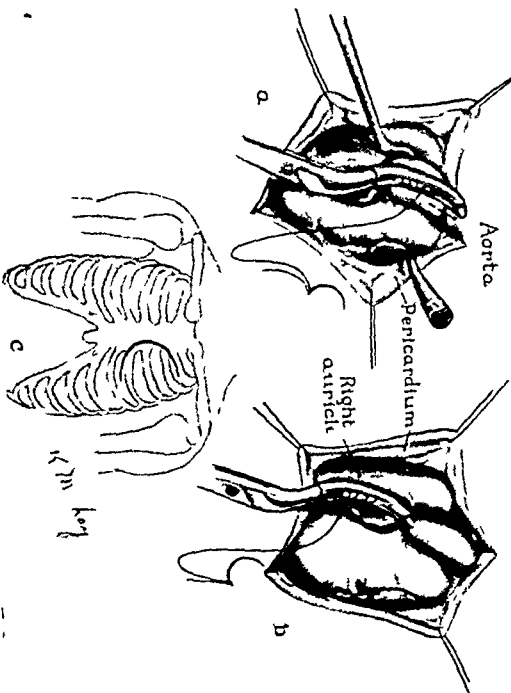


Fig 10—The use of the Trendelenberg probe and clamp in arresting hemorrhage in the auricles and great vessels

FIG 12

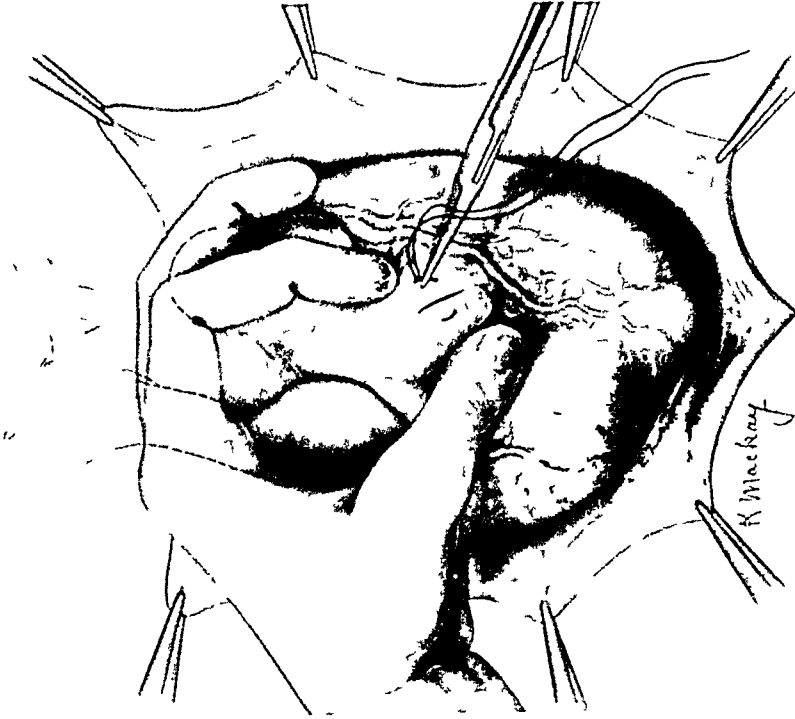


FIG 11



FIGS 11 and 12—The Suerbruch grip, illustrating the method of controlling hemorrhage by compression of the great vessels

duced by knife or ice-pick except one (Case 37), which was caused by a bullet. In no instance was operation not undertaken because of the patient's condition. This means that in several instances the condition of the patient was so serious that there was practically no hope for recovery. No patients were operated upon in which the diagnosis was found to be incorrect, but

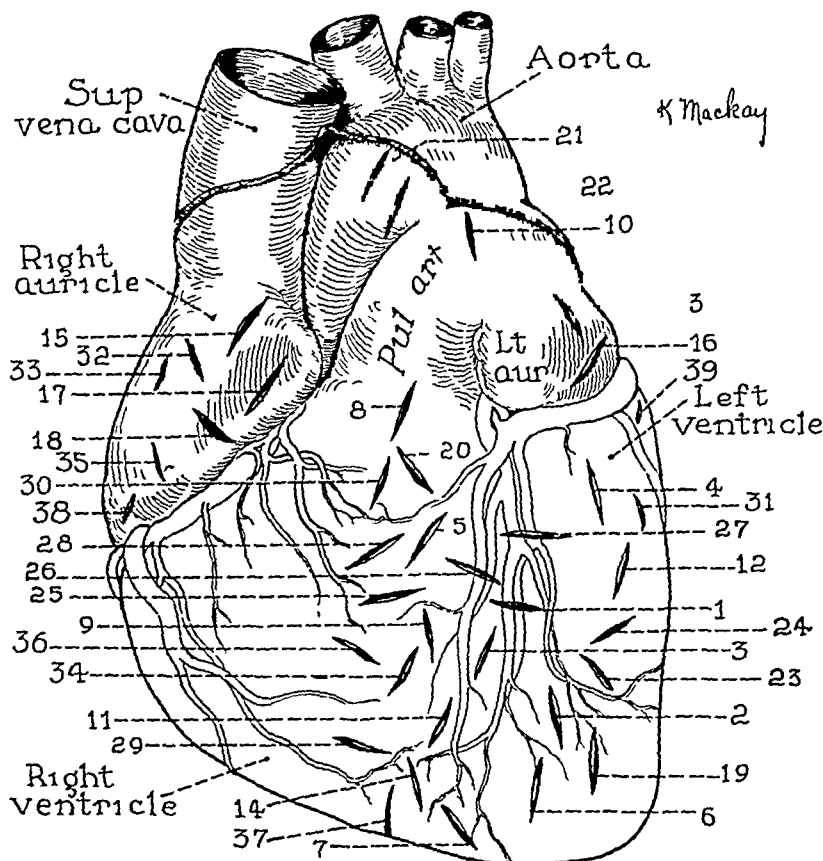


FIG 13—Composite picture showing the approximate location of the heart wounds reported in this paper

it is only fair to say that some patients may have died with cardiac wounds upon whom operation was not performed. In two patients operated upon death occurred because of unnecessarily delayed operation, the result of failure of early diagnosis. There was one death from a postoperative hemorrhage due to the failure to ligate properly the internal mammary artery. The mortality rate in this series of 38 cases has gradually decreased, due, I believe, to the alertness of a Resident House Staff in establishing the diagnosis early and to better teamwork both at the operation and in post-operative care. The position of the right ventricle, occupying the greater part of the anterior portion of the heart, accounts for the fact that 14 of the 38 injuries were in that chamber. That ten of these patients survived is probably due to the fact that the right ventricle is easier to approach and suture. While pericardial adhesions undoubtedly form after these injuries, they are not of such a character as to produce symptoms either by constrict-

tion or by increasing the work of the heart. That an already damaged heart can undergo considerable operative interference has been shown in those patients operated upon for coronary occlusion and for cardiac constriction. One of the patients in this series had been treated previously for myocardial failure. He recovered following the suture of a wound of his heart and is alive two years after the operation (see Tables I, II, and III).

Cardiac Rupture and Contusion—Another type of cardiac injury which undoubtedly occurs with greater frequency than is generally supposed results from crushing wounds, usually from automobile accidents. Many are immediately fatal and are due to rupture of the heart, lungs, or great vessels as a result of compression of the thoracic viscera or penetration of the heart by broken ribs or sternum. Bright and Beck²¹ collected 176 instances of injury to the heart following penetrating wounds of the chest, and have called attention to this type of injury as a common, though frequently overlooked, cause of death.

Certainly, there is no reason to believe that the heart, situated as it is between the sternum and the spine, is not subject to contusions of considerable severity, nor is there any reason to believe that recovery does not take place in the majority of instances. Other organs, notably the kidneys, are frequently the recipient of contusions from which they completely recover. The most common cause of such an injury is an automobile accident, in which an individual is suddenly thrown forward against the steering wheel. The sternum and ribs may be broken, and their ends directly injure the heart, or the sudden compression of the heart may injure it although a break has not occurred (Fig 14).

One can only speculate as to the exact nature of these injuries or as to the manner in which they are produced. In those patients who survive there is probably a contusion of the heart muscle with some hemorrhage into the myocardium, or gross hemorrhage into the pericardium.

Little attention has been paid to nonpenetrating heart lesions which are not fatal. Any patient who is struck in the chest must be suspected of such an injury, particularly if such symptoms as precordial pain, dyspnea, and tachycardia are present. Persistence of these symptoms, together with irregularity of the heart, cyanosis, and a peculiar "tick-tick" quality of the heart sounds, makes the diagnosis almost certain.

Cases of this kind give rise to speculation as to the eventual outcome, and raise many difficult medicolegal questions. Cardiac neuroses and malingering must always be considered, especially where the predominating symptoms develop following an injury to the chest in a patient previously well, it must be assumed that the symptoms are the result of that injury.

The treatment is entirely symptomatic. The chief reliance is to be placed on morphine and sedatives for quiet and rest, and on oxygen for dyspnea and cyanosis. Digitalis may be given but is of doubtful value. Above all, a patient with even a suspected cardiac lesion should be confined to bed until all symptoms have subsided.

CARDIAC TRAUMA

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TABLE I
SUMMARY OF 38 CASES OF CARDIAC WOUNDS

Case No	Sex	Age	Instru- ment	Period from Admission	Location	Result	Cause of Death	Survival Period	Comment
1	M	18	Knife	30 minutes	R ventricle and coronary	Recovery		3 days	Well 8 years
2	M	25	Knife	40 minutes	L ventricle	Recovery	Pericarditis	None	Well 9 years
3	M	41	Knife	30 minutes	R ventricle	Death	Hemorrhage	2 days	Necropsy wound healed
4	M	25	Knife	30 minutes	R ventricle	Recovery	Pneumonia	2 days	Large wound died on table
5	M	30	Knife	60 minutes	R ventricle	Death	Emphysema	14 days	Well 4 years
6	M	21	Knife	Not known	R ventricle	Recovery	Pneumonia	2 days	Necropsy, wound healed
7	M	32	Knife	Not known	R ventricle	Death	Pneumonia	36 hours	Well 3 years
8	M	27	Ice-pick	Not known	R ventricle	Recovery	Bacteremia		Mediastinal emphysema
9	M	24	Knife	Not known	R ventricle	Death			Necropsy not done
10	M	34	Ice pick	Few min	R ventricle	Recovery			Well 5 years
11	M	22	Ice pick	Few min	R auricle	Recovery			Well 2 years
12	M	36	Ice-pick	15 minutes	R auricle	Recovery			Necropsy wound healed
13	M	30	Knife	Not known	R auricle	Death	Hemorrhage	None	Well 2 years
14	M	20	Knife	30 min?	R auricle	Recovery	Infection	None	Necropsy not done
15	M	43	Knife	1 hour?	R auricle	Recovery	Pneumonia	2 days	Well 11 months
16	M	36	Knife	Not known	R ventricle	Death			Necropsy not done
17	M	22	Ice pick	Not known	Aorta	Recovery	Tamponade	None	Well 2 years
18	M	30	Ice-pick	Few min	L ventricle	Death	Hemorrhage	5 hours	Necropsy during operation
19	M	28	Ice-pick	Not known	L ventricle	Recovery			Died during operation
20	M	30	Ice pick	1 hr 30 min	R ventricle	Recovery			Did not react
21	M	36	Knife	1 hr 30 min	R ventricle	Recovery			Well 16 months
22	M	19	Knife	Not known	R and coronary	Recovery			Well 16 months
23	M	24	Knife	Not known	R ventricle	Death			
24	M	24	Knife	Not known	R and coronary	Recovery			
25	M	24	Knife	30 minutes	R ventricle	Recovery			
26	M	39	Knife	Not known	R ventricle	Recovery			
27	M	40	Knife	30 minutes	R ventricle	Recovery			
28	M	39	Knife	Not known	R auricle	Recovery			
29	M	38	Knife	Not known	R and L	Recovery			
30	M	35	Knife	30 minutes	R auricle	Recovery			
31	M	24	Knife	Not known	R auricle	Recovery			
32	M	38	Knife	Not known	R ventricle	Recovery			
33	M	35	Knife	Not known	R ventricle	Recovery			
34	M	38	Knife	Not known	R ventricle	Recovery			
35	M	21	Knife	Not known	R ventricle	Recovery			
36	M	24	Knife	Not known	R ventricle	Recovery			
37	M	19	Ice pick	1 hour	L auricle	Recovery			

TABLE II
CAUSE OF DEATH

	No of Cases
Hemorrhage	6
Pericarditis infection	3
Pneumonia	4
Emphysema	1
Tamponade	2
Total	16

TABLE III
LOCATION OF WOUND

	No of Cases	Pats Recov
Aorta (intrapericardial)	2	1
Pulmonary artery (intrapericardial)	1	0
Right auricle	6	4
Left auricle	3	2
Right and left auricle	1	0
Right ventricle	14	10
Left ventricle	8	3
Right ventricle and coronary	3	2
Totals	38	22

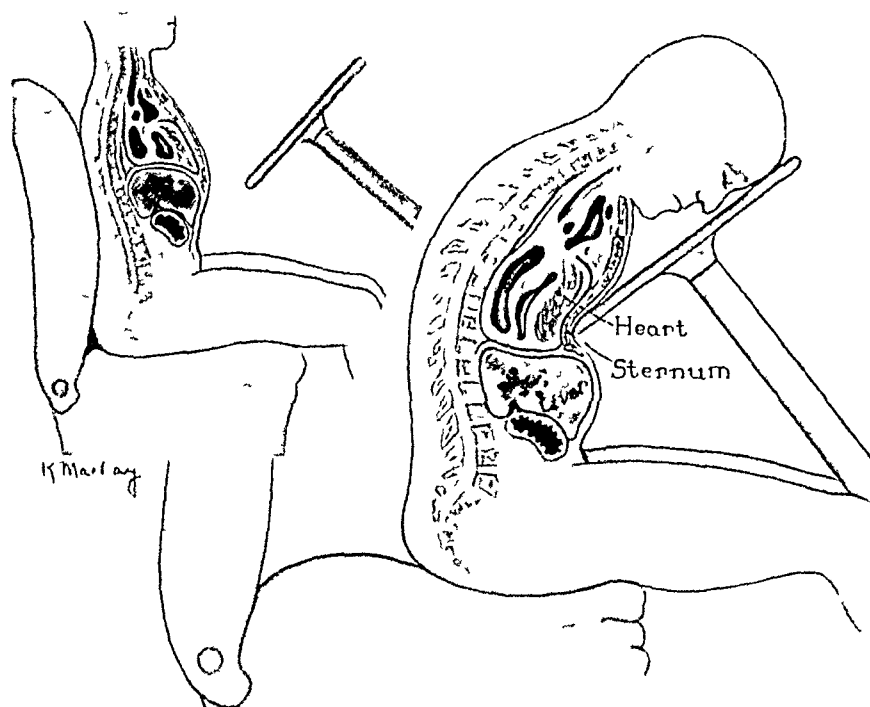


FIG 14—Diagrammatic representation of cardiac injury by the impact of a steering wheel

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AN EFFECTIVE METHOD FOR THE DEVELOPMENT OF COLLATERAL CIRCULATION TO THE MYOCARDIUM*

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A method for the development of collateral circulation to the dog heart was described previously by Heinbecker and Barton¹ (1940) Microscopic studies and perfusion experiments demonstrated that by it an apparently satisfactory collateral circulation could be established The present communication presents evidence that the collateral circulation so produced, can prevent the fatal ventricular fibrillation as well as the gross myocardial infarction which are so frequently encountered after the occlusion of large branches of the coronary arteries

The problem of securing a functional test of the efficacy of collateral circulation to the heart is a difficult one Burchell² (1940) recently, and others, previously, have summarized the results of ligation of the main branches of the coronary arteries in animals by various operators The results have been highly variable both as regards survival rate and the degree of myocardial infarction Any attempt to measure the value of a collateral circulation by determining the mortality rate after ligation of any of the major coronary branches would require the use of a large number of animals, in order to allow a statistical comparison of the results with the better results reported by previous operators Fortunately for our purpose, no one has found it possible to achieve survival in the normal dog following complete ligation, at one sitting, of both branches of the left coronary artery near their points of origin It was decided, therefore, to apply this test to the collateral circulation established by our method It follows that any survivals from such a test would owe their existence to the beneficial effects of the established collateral circulation

Present Method for Producing Collateral Circulation to the Myocardium — Our present method for producing the collateral circulation to the heart involves the introduction into the pericardium of an irritating mixture which causes an adhesive pericarditis At the same operation, the pericardium is attached by sutures to the retrosternal tissues The procedure differs slightly from that which we have previously described, in that a mixture previously prepared is used as an irritant instead of a number of separate ingredients This mixture can be inserted into the pericardial sac through a relatively small

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CIRCULATION TO MYOCARDIUM

MIXTURE TO PRODUCE PERICARDIAL ADHESIONS

Commercial gelatin	32.5 Gm
Aleuronat	32.5 Gm
Starch	50.0 Gm
Glycerin	275.0 Cc
Water	200.0 Cc

Put gelatin, aleuronat, starch, and glycerin into a container. Add boiling water and stir over bath 30 minutes. When the paste is smooth, add 32.5 Gm lionite No. 60 and stir until thoroughly mixed. The mixture is semisolid at room temperature, semiliquid at 38° C.

hole by a grease-gun with a long curved nozzle which can be directed to all parts of the enclosed cavity. After the material is introduced, the pericardium is closed and sewed to the retrosternal tissues by four interrupted silk sutures.

Experiments to Test the Efficacy of the Collateral Circulation—Fourteen animals were prepared in the above manner. Four to 12 weeks after the first operation, the animals were again operated upon and silk ligatures were applied to the anterior descending and to the left circumflex arteries about one centimeter from the aorta. Eight of the 14 animals died in a few minutes, death always occurring after the second of the two arteries was ligated. The remaining six animals, however, tolerated this operation well and they lived in apparent good health for one to three months (Table I). At the end of

TABLE I

Dog No	Date of Establishment of Collateral Circulation	Date of Coronary Artery Ligation	Date of Autopsy	Findings
				Left anterior descending and left circumflex arteries and accompanying veins ligated
B2	3/13/39	6/ 5/40	7/24/40	No gross infarction of myocardium
84	12/22/39	3/13/40	6/ 5/40	No gross infarction of myocardium
77	12/18/39	6/ 5/40	7/24/40	No gross infarction of myocardium
72	12/12/39	6/ 5/40	7/24/40	No gross infarction of myocardium
65	12/ 1/39	6/ 5/40	7/24/40	No gross infarction of myocardium
46	4/24/39	9/23/39	1/ 4/40	No gross infarction of myocardium

this period, they were sacrificed to obtain proof of the adequacy of the ligations. Autopsy revealed that the arteries and their accompanying veins had been completely ligated in all six animals. Examination of the heart musculature showed an absence of gross infarction. Microscopic sections revealed a well-developed pericarditis and heart musculature which appeared normal except for scarring in the immediate vicinity of the ligatures (Fig. 1).

The anterior descending and left circumflex branches of the left coronary artery of 14 control animals were ligated in the same manner. In all instances death, due to ventricular fibrillation, occurred within three to five minutes. In 50 per cent of the cases, fibrillation developed after the ligation of only one artery.

Relative Importance of Extrinsic and Intrinsic Collaterals—In 11 dogs, the mixture was inserted into the pericardial cavity and then a large sheet of

cellophane was placed between the pericardium and the retrosternal tissues. It was held in position by a few interrupted silk sutures. In none of these animals were adhesions found, subsequently, between the pericardium and retrosternal tissues. After a period of one to three months, nine of the

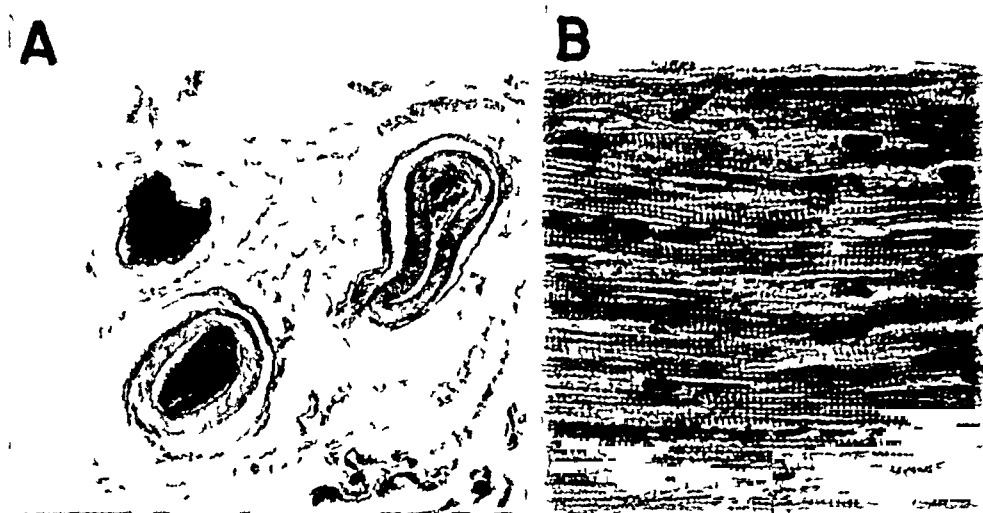


FIG. 1—(A) Photomicrograph of pericardium over anterior surface of the left ventricle of Dog No. P77 after establishment of adhesive pericarditis and attachment of pericardium to retrosternal tissues. Note large blood vessels. Survival after ligation of both branches of the left coronary artery near their origin ($\times 38$).

(B) Photomicrograph of heart muscle of left ventricle of Dog No. P72 2 cm distal to the points of ligation of anterior descending and circumflex branches of left coronary artery near their origin, with survival. Note its normal structure ($\times 390$).

animals were operated upon again, and an attempt made to ligate the anterior descending and left circumflex branches of the left coronary artery one centimeter from their points of origin. All the animals died promptly from ventricular fibrillation, often after ligating only one of the arteries. The remaining two animals were sacrificed without ligation of coronary arteries and the collateral circulation injected with India ink in the manner previously described (Heinbecker and Barton, 1940, *loc cit*¹). In both of these animals many capillaries, filled with ink, were visible in the pericardial adhesions but the inky fluid did not fill the cavity of the ventricles, as is customary in animals where the pericardium also has been attached to the retrosternal tissues. This is regarded as evidence that the degree of collateral circulation is much less in such animals than in those in which adhesions with retrosternal tissues are also present.

DISCUSSION—It is thus possible to produce a collateral circulation to the myocardium of the dog, which is adequate to prevent the degree of ischemia which invariably results in ventricular fibrillation and death when the two main left coronary branches are ligated. Such collateral circulation is also adequate to prevent gross myocardial infarction. By the method employed, additional intercoronary collaterals developed by the pericarditis are not sufficient in themselves to prevent death from such extensive myocardial ischemia. To produce a really effective collateral circulation to the heart, there must be

an extrinsic source, and this should contain large-sized blood vessels in which a high arterial pressure exists. It would also seem to us an additional advantage to have such an extrinsic source remain in its normal environment.

Under our experimental conditions, the insult to the myocardial circulation of the animals was great. It is probable that the degree of myocardial ischemia which can produce pain in man may be much less. It might, therefore, be prevented by much lesser degrees of collateral circulation such as could be afforded by the additional intercoronary capillaries produced by the pericarditis itself. For protection against greater degrees of sudden myocardial ischemia, an extrinsic source of collateral circulation would, doubtlessly, also be required. Only through clinical experience can we obtain actual knowledge concerning the degree of collateral circulation which is necessary to prevent pain and ventricular fibrillation which leads to death from coronary disease in man.

In any attempt to apply the procedure to man, certain problems will at once arise. First, would be the question of the safety of the mixture needed to produce the pericarditis. Apparently, the substance used in the animals can be used in man. In one patient, a mixture of aleuronat, lionite, and sodium morrhuate produced no disturbance of the cardiac rhythm after 15 cc of a 10 per cent procaine solution had been previously placed into the pericardial cavity and allowed to remain for five minutes. This preliminary application of procaine has been advocated by Mautz³ (1936) as a means of diminishing the irritability of the heart muscle and thereby tending to inhibit the development of ventricular fibrillation. In the same case, no appreciable degree of pericardial effusion resulted from the use of 60 cc of the material. The possibility that a pericardial effusion might develop and lead to cardiac tamponade cannot be entirely ruled out, and perhaps should be guarded against by incomplete closure of the pericardial sac. Any leak of material would serve to increase the adhesions between the pericardial sac and surrounding structures, which could only be beneficial. In over 100 animals, in which pericarditis has been produced by the mixture, death from cardiac tamponade resulted only twice. No effort was made to diagnose or treat the condition before autopsy in these two instances.

In the dog, the mobility of the mediastinum is such that the pericardium is readily elevated to the retrosternal tissues. In man, such an elevation will be possible only in cases where there is not much enlargement of the heart. With large, heavy hearts a limited anterior thoracoplasty might be necessary to permit approximation of the pericardium and retrosternal tissues. Experiments are now in progress to determine whether or not an island of retrosternal tissue, with the internal mammary arteries running to it, can be successfully displaced and grafted to the pericardium.

SUMMARY AND CONCLUSIONS

An effective method of producing a collateral circulation for the dog's myocardium is described.

The effectiveness is proved by the fact that following complete ligation, at one operation, of the anterior descending and left circumflex branches of the left coronary artery approximately one centimeter from the aorta, six out of 14 dogs survived. In control animals, such ligations were invariably immediately fatal.

At autopsy, the heart muscle of the surviving animals showed no gross infarction.

On the basis of the experimental evidence, it is felt that, for a maximally effective collateral circulation to the heart the extrinsic source should contain blood vessels of large caliber.

The method should be applicable to the treatment of myocardial ischemia in man.

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THE TREATMENT OF VASCULAR INJURIES *

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A REVIEW of the surgical treatment of vascular injuries seems particularly in order at the present time, since we are confronted with the possibility of entering upon another war.

It is a far cry from the bow and arrow wounds of early Indian wars, through the musketry, rifle, and cannon-shot injuries of the Revolutionary, Mexican, and Civil wars, the steel-jacketed bullet wounds of the Boer and Spanish-American wars, the high explosives and gas injuries of the World War, to the wounds of mechanized and airplane warfare of the present conflict.

Though the nature of wounds in wars of varying periods has differed greatly, all serious wounds have been characterized by three outstanding features, namely, pain, shock, and loss of blood. To this unfortunate combination is due most of the morbidity and mortality of the casualties of combat.

Transfusion—The most striking advance in the surgical treatment of the wounded has been directed toward the relief of shock and hemorrhage, and has been brought about by improvements in transfusion service.

From his book on Transfusion, published in 1922, by Dr. Geoffrey Keynes, an honorary member of this Association, I quote the following: "During the first two years of the World War almost nothing was known in the British Army of its possibilities. I have no evidence that the French or German Army doctors were any better informed than ourselves. Some attempt was made, in 1916, to introduce the use of direct transfusion through cannulae, but the technic was too difficult and uncertain for the stress of war conditions. It was not until 1917, when the British Army Medical Corps was being steadily reinforced with officers from the United States of America, that knowledge of blood transfusion began to be spread through the armies."¹

Again, concerning the vagueness of indications for transfusion, from the work on Gunshot Injuries of the Blood Vessels by Major General George H. Makins, Senior Consulting Surgeon to the British Expeditionary Forces in France, published in 1919, I quote the following: "With a moderate hemorrhage there is no need to replace the lost blood artificially. If the bleeding has been severe, the loss can be made good by a more easily obtainable fluid, i.e., 6 per cent gum arabic solution. A precise indication as to when blood transfusion is imperative is still wanting and much to be desired. Most observers agree that a critical point has been reached when the total hemoglobin content is as low as 30 per cent."²

These comments on transfusion in the British Army in the World War

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are in striking contrast to the situation which exists in England to-day. Doctor Philip Wilson, who has recently returned to this country after having established an American Orthopedic Service in London, has given an interesting account of the operation of transfusion service in the London hospitals, from which I have made the following brief extract:

"All these hospitals are regularly supplied with citrated blood, plasma, and dried serum from one of the four blood depots organized by a committee of the Medical Research Council." At the hospital with which his group was associated, and this is the routine with others, he says: "The supply truck called regularly every Monday and delivered 12 half liters of blood and took away the unused remainder of the blood that has been left from the previous week to be converted into plasma. The blood supply service also replenished the stock of plasma and dried serum and kept it up to an agreed level."³

This service can be duplicated wherever there is need. In the Spanish Civil War, similar blood transfusion centers were established and transfusions were extensively used. It is estimated that 10 per cent of the wounded could be saved through this agency.

It is safe, therefore, to claim that the soldier who has the misfortune to be seriously wounded at the present time, has less to fear from shock and hemorrhage, by reason of the availability of transfusion, than at any time in any previous conflict.

Classification in Regard to Indication for Treatment—In considering the indication for treatment, vascular injuries fall into three general classifications:

- (1) Those which demand immediate repair
- (2) Those in which delay at least for a brief period is permissible
- (3) Those which, for various reasons, come under observation at a late period. These will consist mainly of traumatic aneurysms and arteriovenous communications.

Hans von Haeberer has made valuable contributions to the literature of vascular injuries, founded on his experience on the German side in the World War. He summarizes the rules to be followed in advanced front line units in dealing with injuries to the extremities as follows:

- (1) Amputation should be carried out when there is no chance to preserve the limb or its functional value.
- (2) Ligation of bleeding vessels in the wound or at the site of choice should be practiced when restoration of the limb can be expected.
- (3) When hemorrhage is not threatening, it may be controlled by a compression bandage. If an Esmarch's bandage is employed, it should not be left in place longer than from one to three hours.
- (4) In smooth gunshot wounds without laceration of the soft parts, when the hemorrhage stops soon, the artery should not be searched for but the wound should be left alone so that an aneurysm may be formed.

Continuing further, he says "Following the injury of a main artery, in the absence of extensive laceration of the soft parts the external hemorrhage may stop rapidly and spontaneously, due to the fact that the various layers have different degrees of elasticity, and by their displacement, obstruct the path of the hemorrhage. Consequently, an hematoma forms in the soft parts and reduces further hemorrhage by compression of the bleeding artery. A pulsating hematoma will be produced, and it represents the precursor of a false aneurysm. The development of an aneurysm of this type should be one's aim, since its surgical treatment, carried out at least 12 days after injury and preferably during the third or fourth week, has proved very successful."⁴ Venous bleeding can usually be controlled by a compression bandage.

Delayed Operations—Those who have survived the immediate effects of vascular injury and who are, in a measure, convalescent, may be evacuated to base hospitals where the facilities for observation and treatment are similar to those provided in well-organized civilian hospitals.

As previously noted, von Haberer advises that traumatic aneurysms be not operated upon until the twelfth day, and, preferably, during the third or fourth week. The British and French were inclined to a longer delay. Makins prefers a delay of two or three months and Matas holds the same opinion. Mont Reid⁵ believes that arteriovenous fistulae should not be operated upon for six months after injury, and offers the following reasons in support of his opinion:

"In some cases, hemorrhage, increasing hematoma, infection, and, very rarely, acute cardiac symptoms make it necessary to operate soon after injury. When none of the foregoing complications make operation imperative, delay presents the following advantages:

- (1) A good collateral circulation develops which permits excision of the fistula without fear of gangrene.
- (2) The injured vessels become thoroughly healed, making their dissection easier and safer.
- (3) Infection is less likely to occur.
- (4) Spontaneous healing may take place."

Most of these advantages apply to aneurysms as well as to arteriovenous communications.

Dangers Inherent to Ligation of Arteries—In wounds of major arteries, the question of ligation or repair, immediately or at a later date, will come up for consideration.

Leriche and Weirquin⁶ list the disturbances following ligation as:

- (1) Mechanical syndrome, varying from massive gangrene down to localized necrosis in muscle causing orthopedic troubles later on.
- (2) Functional disturbances, such as cyanosis, trophic disorders and muscular paralysis.

The ideal prophylaxis against these dangers is the substitution of suture

for ligation, which they consider generally impossible in war wounds, and which has limitations which we shall presently discuss

It is obvious that ligation in the presence of exsanguination, with attendant low blood pressure, vastly increases the likelihood of massive gangrene, hence the necessity for adequate transfusion for replacement of lost blood and for restoring and maintaining blood pressure

Since many ligations are imperative, it is important to consider recent experimental and clinical investigations which have developed methods for increasing their safety

Measures for Increasing the Safety of Ligations—Gage and Ochsner,⁷ in a recent paper, suggest a number of measures which are necessary for successful arterial ligation. These have to do with the establishment and maintenance of efficient collateral circulation. They are classified under three heads: (1) Spontaneous, which occurs in arteriovenous aneurysms; (2) Mechanical, which may be accomplished by the Matas' compressor, intermittent venous occlusion, including the Paevex machine, and simultaneous ligation of the concomitant vein; (3) Physiologic, which results from chemical section of the cervicodorsal and lumbar sympathetics, by novocain or alcohol block.

They were so favorably impressed with the physiologic method of preventing ischemic gangrene in ten cases of ligation of major peripheral arteries, and in four cases of emboli in the femoral arteries, that they prefer it to all other measures.

Leiche and Weirquin⁶ have studied the effects of arterial ligation upon the vasomotor system. According to their observations, 'a ligation acts as a severe trauma and produces reflex vasoconstriction distally. This reflex is removed by resection of the obliterated length of the affected artery. The reflex can also be abolished by arterial section between ligatures, by periarterial sympathectomy above the lesion, by anesthetic infiltration of the adventitious coat, by regional infiltration of the sympathetic system, or by ganglionectomy.'

They⁶ advise limited resection of artery between ligatures, maintenance of blood pressure to help the rapid flow of blood back into the limb, periarterial sympathectomy above the lesion, or section of the regional sympathetic plexus.

"It is important to remember that if infiltration is to be undertaken, it must be done at once. Delay is fatal, because tissues die quickly." With the employment of these safeguards, they hold that "ischemic gangrene should no longer be inevitable, and the risk attending arterial ligation should be much lessened."

In keeping with what we have just quoted from Gage and Ochsner, Leiche⁶ says "Infiltration of the cervical or lumbar sympathetics is more necessary than warming the patient with cotton-wool or with radiant heat. It is not the skin that wants the warmth so much as the deep tissues."

Arterial Suture—Arterial suture is the ideal method of preserving the

circulation in distal parts which ligation might jeopardize. Except under most favorable surroundings, in clean wounds, and, preferably, in those in which the tissues have completely healed, suture is prone to be followed by immediate thrombosis or delayed aneurysmal formation, hence, Leriche points out that suture is generally impossible in acute war wounds. In civil practice, operating under favorable surroundings, and usually in delayed cases, suture has proven very successful.

Very little has appeared, so far, in the literature concerning the treatment of traumatic aneurysms and arteriovenous communications in the present war. At a later and quieter period, this subject will, no doubt, receive the attention which its importance demands.

Bumm, a German surgeon, discusses "pulsating hematmata or spurious aneurysms as a sequel to war injury" and reports seven cases from the present conflict. He says "Generally speaking, suture should be attempted when there is danger of untoward consequences from ligation. Suture is contraindicated in severe infection but may be used with a high degree of safety in the presence of light infection provided loose tamponade is applied for the purpose of diamege"⁸

From the English viewpoint, based on his World War experiences, Mitchiner⁹ writes discouragingly of reparative vascular surgery. "Under war conditions, the results of reparative surgery on blood vessels are notoriously disappointing. In a certain number of repair operations which he performed, some two-thirds thrombosed at once, but not a limb was lost. The remaining third maintained circulation. Three years later several of these cases were seen again. All those whose vessels had thrombosed were well and at work, while of those whose circulation had endured, nearly all had aneurysms."

Hans von Haberer, whose experience is extensive and whose views are sound, gives the following advice:

"Suture of an artery should not be performed in cases in which the artery could be ligated without damage to the nutrition and function. This holds true for the external carotid and its branches, and for those peripheral arteries which supply their areas in pairs, such as the radial and ulnar and the anterior and posterior tibials. Suture is especially indicated in the internal and common carotids, the axillary, subclavian, and brachial, external and common iliacs and popliteal, and the femoral above the origin of the profunda."

He reports that he has operated upon 251 aneurysms, with 182 sutures, and 69 ligations, and considers the danger of thrombosis to be slight. There were 14 deaths—12 from septicemia from multiple injuries, two from shock and hemorrhage. Six deaths were in the suture group. There were three amputations and one recurrence of the aneurysm. In ligations he recommends the intrasaccular method of Kikuzi and von Füssch.⁴ This does not differ in any respect from the endo-aneurysmorrhaphy of Matas, introduced in 1888, and practiced universally since that date.

Heparin—The introduction of heparin gives promise of great therapeutic value in vascular surgery Murray and his associates¹⁰ have made interesting reports of their experimental and clinical experiences with its continuous intravenous use in arterial and venous suture, venous grafts, embolectomy, mesenteric thrombosis, pulmonary embolism and thrombophlebitis.

Whatever dangers may attend arterial suture in acute war wounds, those cases which are delayed, and which do not require early operation, may still be given the benefit of suture with much prospect of success.

Arteriovenous Aneurysms—An entirely new conception of the pathology as well as of the indications for operation in arteriovenous fistulae, has resulted from studies upon cases encountered in the World War and confirmed by clinical and experimental observations in civil practice.

The investigations of Gundermann, Caro, Makins, and Cazamian, carried on between 1915 and 1917, established the fact that arteriovenous fistulae between larger vessels results in definite and progressive heart damage. Reid while working with Halsted, between 1914 and 1916 says "In the course of two or three years, we became fully convinced that a fistula between the larger vessels of the neck or legs may cause marked hypertrophy and dilatation of the heart, and, in some instances, cardiac decompensation and death."¹¹

This feature of an arteriovenous fistula is an added indication for operation, and, in many instances, the most compelling one.

Its importance was brought to the attention of the profession in 1923 by Matas,² in a paper entitled "The Systematic or Cardiovascular Effect of Arteriovenous Fistulae", and again, in 1931, by Reid,¹¹ in a paper entitled "The Effects of Arteriovenous Aneurysms upon the Heart."

In uncomplicated cases, delay in operation for from four weeks (von Haberer) to six months (Reid) is desirable for reasons already set forth.

In cases of long standing, certain changes in the involved vessels, the collateral circulation, and the heart will usually have taken place. In the vein distal to the lesion, varicosities are frequent, in the artery proximal to the lesion, degeneration of the walls and dilatation of the lumen are often observed, in the heart, degenerative changes of varying degree are found. In all instances, an efficient collateral circulation is rapidly developed. Quadruple ligation and excision is indicated in these cases.

In early cases in healthy individuals transvenous arterial suture is the method of choice in accessible fistulae. The ideal method would seem to be the separation of artery and vein with suture of the opening in both vessels, but Reid¹¹ points out that this measure has been followed by serious pulmonary complications, due to embolism of air and of blood clots from thrombosis at the site of operation. He considers that ligation of the vein is a safer procedure, and that it probably results in a better balance between arterial and venous beds, even though the artery is restored.

In cases of long standing, Matas,¹² and also Holman, advises that intermittent closure of the fistula by digital or mechanical pressure be practiced.

for a time, in an attempt to prepare the heart for the shock of permanent closure of the fistula which it might not otherwise be able to withstand

Early Cardiac Decompensation in Arteriovenous Aneurysms Palliative Operation—Few cases of early cardiac decompensation are on record. Mason, Graham and Bush report a traumatic arteriovenous aneurysm of the left subclavian vessels, not subjected to operation, that died on the fourth day from cardiac decompensation, as proved at autopsy. In this paper, four cases were abstracted from the literature, reported by Tixier and Arnulf, Rochei, Harvey Stone, and Caraven, in which serious cardiac disturbance or decompensation was noted by the fifth day in three instances, and by the fifteenth day in one instance.

As a temporary measure to relieve the embarrassed heart, Tixier and Arnulf suggest that the vein be ligated some distance proximal to the fistula, a curative operation to follow at a later date. The benefits of proximal ligation of the vein have been observed by Stone and by Holman, and Matas considers it a measure that should be helpful.¹⁴

Pulsating Exophthalmos—Pulsating exophthalmos results from an internal carotid-cavernous sinus fistula. Approximately three-fourths of the cases are caused by trauma, and the remaining fourth by rupture of latent congenital or acquired aneurysms of the internal carotid or of arteriosclerotic patches on its wall. The treatment has been varied and the results uncertain.

Approaching the subject from the neurosurgical standpoint, Dandy has successfully treated two cases in which the internal carotid had previously been ligated in the neck without success, by occluding the intracranial portion of the artery by the application of a silver clip after it has emerged from the cavernous sinus and just before its division.

A perusal of Dandy's¹⁵ paper, presented at the fifty-sixth meeting of the American Surgical Association, and of the discussion, which was taken part in by Doctors Matas, Naffziger, and Mont Reid, gives one a comprehensive review of the methods which have been employed in the treatment of this peculiar lesion.

Wounds of the Heart—Writing from London, Mitchiner⁹ says "Under conditions pertaining in war—wounds of the heart, great vessels, and even the proximal ends of the limb—vessels are usually so rapidly fatal, either from primary hemorrhage or from gross damage to neighboring structures, that the patient seldom reaches the surgeon alive."

With present facilities for the treatment of shock and hemorrhage, together with airplane ambulance service and automobile-trailer operating units which the United States Army may install, we expect that some heart wounds will be successfully operated upon. In civil practice, successful cardiorrhaphies are being reported from every section of the country. The diagnosis of cardiac tamponade can be made with reasonable certainty, and in a brief period of time, by noting the location of the wound, the shock, low arterial blood pressure, and quiet heart. On reaching the hospital, the diagnosis can be confirmed by fluoroscopy of the heart, which will reveal the

absence of pulsations, and by finding a high venous pressure. The time element is of greatest importance, and if tamponade can be quickly relieved, the patient has an excellent chance for recovery when the wound has been sutured.

In the Hillman Hospital, during the past five years, 20 stab wounds of the heart have been operated upon by various members of the attending staff. The average time from infliction of injury to beginning of operation was one hour and 40 minutes. Six patients recovered and 14 died, six of these on the operating table. This recovery rate is by no means as good as is reported from other clinics, but it is worthy of record, since no case had been successfully operated upon in this institution previous to October, 1935.

Vascular Injuries in Civil Practice—While, fortunately in no way comparable to the great number of vascular traumata which occur in war, there is no lack of such clinical material in civil practice. To every large hospital which receives accident patients, sufferers from vascular wounds continually present themselves. It is a sad commentary on the present state of society that practically all these injuries result from personal altercations or conflicts with officers of the law.

Since 1932, a series of vascular injuries of major importance, 29 in number, have come under my care. They have presented the following conditions (Table I).

TABLE I

TYPES OF VASCULAR INJURIES SUSTAINED

Arteriovenous aneurysms	19
Traumatic aneurysms	1
Gunshot wounds of brachial artery	1
Cirroids of scalp (traumatic)	2
Stab wounds of the heart	2
Extensive hematoma from rupture of femoral vein and branches	1
Total	29

TREATMENT AND RESULTS

	No	Recovered	Died
<i>Arteriovenous aneurysms</i> (19)			
Quadruple ligation and excision	7	6	1*
Transvenous suture	2	2	
Lateral suture of artery ligation of vein	2	2	
Recovered without operation	2	2	
Sudden death—fourth day. No operation	1		1
Refused operation	3		
Lost sight of while waiting for time for operation	2		
<i>Aneurysms</i> (4)			
Ligations—Common carotid	1	1	
Brachial	1	1	
Endoaneurysmorrhaphy—Femoral	1	1	
Lateral suture—Femoral	1	1	
<i>Cirroids of scalp</i> —Multiple ligation and excision	2	2	
<i>Gunshot wound of brachial</i> —Ligation	1	1	
<i>Laceration of femoral vein</i> —Ligation	1	1	
<i>Stab wounds of heart</i> —Cardiorrhaphy	2		2

* One quadruple ligation and excision died from intercurrent disease after the wound had healed. One patient died six years after operation from cardiac decompensation due to a common carotid—left innominate fistula not found at original operation.

VASCULAR INJURIES

SUMMARY

The treatment of vascular injuries is discussed under the following headings

- (1) The great improvement in the treatment of shock and hemorrhage brought about by developments in transfusion since the World War
- (2) Classification of vascular injuries in regard to treatment
 - (a) Those which demand immediate treatment
 - (b) Those in which a brief period of delay is permissible
 - (c) Those which come under observation at a late period
- (3) Dangers inherent to ligation of arteries, especially in patients already exsanguinated
- (4) Measures for increasing the safety of ligations
- (5) Suture *versus* ligature
- (6) Traumatic aneurysms and arteriovenous communications
- (7) Wounds of the heart
- (8) Vascular injuries in the current war
- (9) Experience in civil practice

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DISCUSSION.—DR DANIEL C EIKIN (Atlanta, Ga) Doctor Mason has imply covered, in the short time allotted to him, his very important subject and, therefore, I will only emphasize the points which he brought out

In the first place, it must be remembered that an hematoma in itself may be injurious by cutting off lateral circulation, and sometimes it may be advantageous to remove the hematoma, even though ligation of a major vessel will then have to be carried out. Ligation of accompanying veins should certainly be done where a major artery is ligated, and temporary sympathectomy by novocain or alcohol may likewise be employed to advantage. The ligation of the proximal vein in an arteriovenous fistula where heart failure threatens, as in large fistulae may be life-saving.

I quite agree that quadrant ligation and excision after a period of three to six months is the procedure of choice in the treatment of an arteriovenous fistula, since it allows time for the development of collaterals, and recurrence of infection is less likely than by any other method.

It must be borne in mind that cirroid aneurysm is frequently initiated by trauma, particularly trauma to a port-wine blemish, and excision of such tumor should be carried out as soon as it is discovered.

RADICAL OPERATIVE TREATMENT FOR SUPPURATIVE PHLEBITIS, AND ITS RESULTS

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PHLEBITIS of the lateral sinus producing bacterial invasion of the blood stream is the classic example of an acute infection of the wall of a vein that is subjected to direct surgical treatment. Operations on the lateral sinus, with a view to the elimination of the infection of the blood stream, have been practiced for many years. Worth while results have been achieved despite the fact that difficulties which are peculiar to the otitic field are encountered. On the other hand, virtually no efforts have been made, according to the literature, to match the results obtained in operations for phlebitis of the lateral sinus by operations on other venous trunks which are similarly affected elsewhere. This appears to be a fact despite the comparative ease of operative exposure of some of these venous trunks and the greater likelihood which often exists of eradicating surgically the source of the invasion of the blood stream in such cases.

The reason for the apparent rarity of operative procedures for acute suppurative phlebitis of readily accessible veins such as the femoral or axillary must be found either in the assumption that they rarely are involved or that involvement by phlebitis rarely is the cause of the clinical picture of septicemia. Therefore, attention should be called to certain observations which have already been reported. In a study made in 1934, of 150 cases of septicemia with positive blood cultures, we¹ showed that acute phlebitis was demonstrable in almost one-half of all cases. It was probably present but not demonstrable for various reasons in many of the remaining cases. The area of phlebitis usually was situated in the main venous trunk in the affected region, such as the internal jugular, the popliteal, or the external iliac veins. In other words, phlebitis when present was to be found in some substantial vein regardless of whether or not its origin from some smaller venous radicle was demonstrable. Suppuration in adjacent soft parts was often found as the source of the infection of the vein. Phlebitis usually was extensive at the time of fatal termination, but even then (at autopsy) the lesion was capable of surgical eradication in not a few instances. The lesion of the vein most often was a suppurative thrombophlebitis, but acute phlebitis without thrombosis was not rare. The mortality in the 150 cases was exceedingly high. Thus, evidence was advanced a number of years ago to show that septic invasion derived from acute phlebitis of main venous channels in surgically accessible regions was not rare, and that the mortality attendant upon so-called conservative treatment of the lesion of the vein was exceedingly high. There is no present reason to materially alter this view, except insofar as specific chemotherapy is concerned. The clinical picture of septic invasion of the blood stream has been profoundly affected, the mortality has

been lowered, metastatic foci are rare, but according to personal observation, the incidence of suppurative phlebitis from which septic invasion of the blood stream may be derived, has not been greatly lowered.

Only brief reference need be made to some of the clinical features of acute phlebitis of the variety under discussion. There appear to be certain sites of predilection, the outstanding one being the axillary vein. In phlebitis derived from lesions in soft parts, there is present an abscess or suppurative lymphadenitis adjacent to the lesion in the vein or less frequently a cellulitis without areas of suppuration. The inflamed vein usually cannot be felt. Prostration is out of proportion to the apparent lesion, that is the abscess. Fever and prostration persist after adequate surgical drainage of such an abscess or similar suppurative focus. Chills, of course, are of sinister significance. However, it should be pointed out that they do not occur in many cases of proven phlebitis.¹

Omitting a detailed consideration of the significance of blood cultures in the diagnosis of and operative indications for suppurative phlebitis, there are two points which I wish to make and which are exemplified in the tabulation of the operative cases. First, blood cultures not infrequently are negative in the presence of suppurative phlebitis amenable to surgical therapy, and secondly, there was no mortality among the operative cases with negative blood cultures. In the absence of a positive blood culture, an absolute diagnosis of suppurative phlebitis can rarely be made. On the other hand, as illustrated by Cases 4, 5, and 7 in Table I, the mortality inevitably will be high if an absolute diagnosis is awaited before proceeding with a surgical effort at cure.

TABLE I
CASES WITH POSITIVE BLOOD CULTURES* (NINE CASES)

Case No	Local Pathology	Pathology of Vein	Chills	Result	Factor in Mortality
1	Cervical abscess	Acute phlebitis with thrombosis of internal jugular vein	Chill	Recovered	
2	Axillary abscess	Suppurative thrombophlebitis of axillary vein	Chills	Recovered	
3	Pelvic cellulitis	Suppurative thrombophlebitis iliac vein	None	Recovered	
4	Cellulitis of hand and forearm	Acute thrombophlebitis of several veins of forearm	None	Died	Delayed therapy of phlebitis
5	Furuncles of lip and nose	Purulent thrombophlebitis of facial vein	Chills	Died	Late case. Metastases present
6	Hemorrhagic infiltration of axilla	Necrosis and thrombosis of axillary vein	None	Died	Fulminating course
7	Axillary abscess	Severe thrombophlebitis of axillary vein	Chills	Died	Delay after drainage of abscess
8	Cellulitis of neck and chest	Subacute proliferative phlebitis of axillary and subclavian veins	None	Died	Vein not accessible for excision
9	Lateral sinus thrombosis. Cellulitis of neck	Thrombophlebitis of internal jugular vein and phlebitis of innominate vein	None	Died	Vein not accessible for excision

* *Streptococcus hemolyticus* (Beta) Cases 1 2 3 7 8 9 *Staphylococcus aureus* Cases 4 5, 6

SUPPURATIVE PHLEBITIS

TABLE II

CASES WITH NEGATIVE BLOOD CULTURES (EIGHT CASES)

Case No	Local Pathology	Pathology of Vein	Chills	Result
10	Axillary abscess	Organizing thrombo and periphlebitis of axillary vein	None	Recovered
11	Suppurative axillary lymphadenitis	Acute periphlebitis of axillary vein	Chills	Recovered
12	Axillary cellulitis	Organizing periphlebitis axillary vein	Chills	Recovered
13	Cervical abscess	Acute purulent phlebitis and periphlebitis of external jugular vein	None	Recovered
14	Suppurative axillary lymphadenitis	Acute phlebitis and thrombosis of axillary vein	None	Recovered
15	Axillary abscess	Acute suppurative thrombophlebitis of axillary vein	None	Recovered
16	Cellulitis of foot	Acute purulent phlebitis and periphlebitis dorsal vein of foot	Chill	Recovered
17	Axillary cellulitis	Acute phlebitis of axillary vein without thrombosis	Chilliness	Recovered
BLOOD CULTURES NOT TAKEN (TWO CASES)				
18	Cervical abscess	Acute phlebitis without thrombosis of internal jugular vein	Chill	Recovered
19	Abscess of foot	Acute phlebitis and periphlebitis dorsal vein of foot	None	Recovered

Current methods of treatment of assumed or suspected cases of suppurative phlebitis can be summarized by stating that they consist of chemotherapy and of surgical drainage of a local abscess when it exists. Proximal ligation of the vein draining a suppurative focus appears to be favored by some authors. It is the direct attack on areas of surgically accessible phlebitis which I wish to advocate anew at this time. The procedure is not advocated for all cases. There are instances in which the lesion is inaccessible, and others in which an attempt at its eradication may be too hazardous. There are, however, cases in which involved veins are accessible surgically, the involvement is of limited extent, and complete excision is possible. As has been pointed out elsewhere,² nothing short of the removal of the segment of vein bearing the area of phlebitis will suffice. Since the problem that is faced is one in which life is in jeopardy, the possible damage as the result of excision of main venous trunks, specifically those of the extremities, is of secondary importance. In fact, however, experience has shown that there are insignificant, if any, ill results from the excision of such trunks. Thus, there may be complete absence of edema of an extremity following excision of sections of the axillary or of the external iliac veins. Another objection which has been made to the proposal to deal directly with areas of phlebitis has been the danger of opening up fresh avenues of infection. Although this undoubtedly is valid, theoretically, there have been no instances in actual practice in which untoward effects could be ascribed to this factor.

The principle of operation consists in adequate exposure of the suspected or obviously involved venous trunk and its excision beyond the visible limits of phlebitis, whenever possible. An examination of the tables will show that the vein was the seat of a suppurative thrombophlebitis in all cases with positive blood cultures. Thus, the lesion was readily discernible when the affected area of the vein was exposed at operation. On the other hand, the lesion

was not obvious in some of the cases with negative blood culture, and the question of management of the vein therefore, requires special consideration in this group of cases. It is not only possible but probable that recovery might have ensued without excision of the vein in some cases in this group and the procedure, therefore, appears more debatable than in cases with positive blood culture.

The influence of chemotherapy on pyogenic sepsis is so profound, so many extraordinary recoveries take place to-day in cases which would have been fatal yesterday, that there is an almost unavoidable tendency to await the effect of chemotherapy alone in any case of pyogenic sepsis. In the present series of operated cases as well as in cases which did not come to operation are instances in which suppurative phlebitis was present and presumably had progressed despite specific chemotherapy. A few may be instances in which patients survived as the result of chemotherapy and in which a more or less localized phlebitis had the opportunity to develop, so to speak, because of survival. In any event, until evidence to the contrary is advanced, one must assume that sepsis due to suppurative phlebitis will or may persist despite chemotherapy and that, therefore, surgical measures for the eradication of the phlebotic process are warranted.

From a study of the tables it is evident that the best results can be anticipated in relatively early cases. At times good results will be obtained even in the severe and advanced lesions, and an effort at eradication of the infective focus in the vein should not be withheld even in the presence of already existent metastatic foci. The clinical condition and the possibility of eradicating the feeding focus are better guides to prognosis than the number of colonies in a positive blood culture. A negative blood culture should not lead to the conclusion to withhold operative intervention if there is clinical evidence to warrant exploration of a vein. A properly conducted exploration of a vein if negative, is not harmful, whereas an overlooked phlebitis or one treated conservatively because the classic picture does not present itself, may lead to a fatal issue.

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HEPARIN ADMINISTRATION¹

METHODS AND RESULTS IN THIRTY CASES

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DURING the past two years, 30 patients have been treated by general heparinization in the Henry Ford Hospital. In a previous paper,¹ the results in the first 11 cases were presented, a resume of the history of heparin was given, and the various indications for heparin therapy were discussed. The literature on the subject of heparin has become large, as will be seen from the bibliographies appended to the review by Mason² and the monograph by Jorpes.³ The largest clinical experience has been that of Murray⁴ and others, at Toronto, where more than 700 patients have been treated with the material.

In this series of 30 cases, heparin was administered for the following conditions: (1) Postoperative embolism which was not immediately fatal, 24 cases, (2) embolism of a peripheral artery with embolectomy, three cases, (3) luetic thrombosis of the posterior tibial artery, one case, (4) hemiplegia from occlusion of the common carotid artery, one case, and (5) phlebitis, one case.

The gross results will be summarized at this time. Twenty-two of the 24 embolism patients recovered. The two deaths will be analyzed below, one of them apparently represents a failure of heparin in the dosage employed to prevent the recurrence of embolism. The circulation was restored to the legs in two of the embolectomy cases, the third lived only a few hours after an attempted removal of clots from the femoral artery. No flow of blood was obtained, and the grave condition of the patient, who was in the terminal stages of arteriosclerotic heart disease and appeared to have mesenteric embolism also, caused the operative interference to be interrupted without an abdominal approach to the iliac artery. A gratifying result was obtained in the case of luetic thrombosis of the posterior tibial artery,¹ and the one case of phlebitis showed transient amelioration. The patient with hemiplegia from occlusion of the common carotid artery was not benefited by heparinization, and expired.

The general plan of heparin treatment is to elevate the clotting time of the blood to an arbitrary optimum level, in the hope that dangerous clotting may be inhibited. The usual method is to administer the material in a continuous intravenous drip. Under ideal circumstances, this results in a prolongation of the clotting time which neither goes far above nor far below the optimum level. Chart I shows what might be termed an ideal heparin

* Read at the First Annual Assembly of the Central Surgical Association, Ann Arbor, Mich., February 28-March 1, 1941.

reaction, with the clotting time being kept at approximately 15 minutes (capillary blood in capillary tubes) by the administration of slightly more than 1 000 units of Connaught heparin per hour. The term "2 per cent solution" on the chart indicates that one 10 cc vial of heparin was added to each 500 cc of physiologic saline solution. One hundred milligrams of crystalline heparin is contained in each 10 cc vial. Hence, the patient received about 1,200 cc of physiologic saline solution daily.

Chart 2 is included to show two things: first, the results of a clinical trial of a brand of heparin prepared in this country (Liquaemin, Roche-

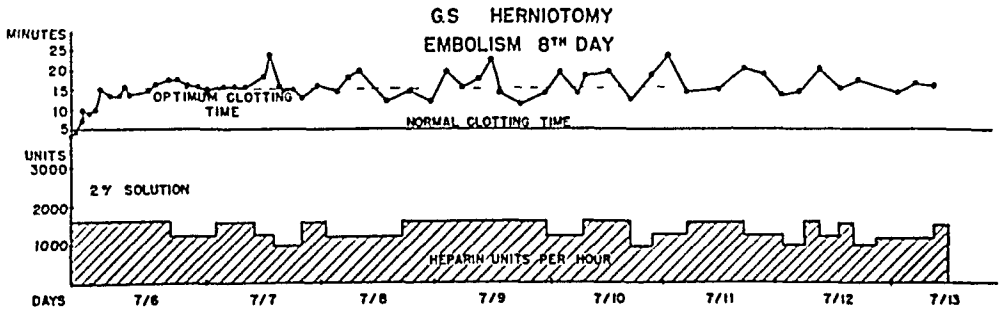


CHART 1—Heparin chart of patient showing good response of clotting time to the administration of approximately 1 000 units of heparin per hour.

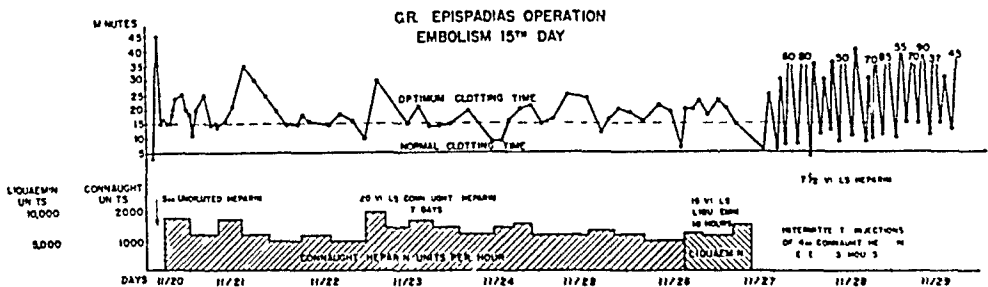


CHART 2—Heparin chart showing the potency of the Liquaemin brand of heparin and the effect of repeated injections of undiluted Connaught heparin.

Oiganon), and second, the effect of intermittent injections of the undiluted material. At that time, Liquaemin was marketed in 5 cc vials, containing 10,000 units, but this unit is of a potency of only one-fifth that of Connaught heparin. Therefore, five vials (25 cc) of this material were needed to produce the effect of one 10 cc vial of Connaught heparin. Recently Liquaemin has been dispensed in a 10 cc vial containing 100 mg of heparin.

Chart 2 also illustrates the effect of intermittent injections at intervals of three hours. McClure and I¹ showed that it was possible to do this without dangerous bleeding. The case reported developed embolism after prostatectomy, and received a course of heparin by the usual continuous intravenous route. Five days after the heparin was discontinued, he had a second small embolism. On account of the presence of mild cardiac decompensation, it was deemed inadvisable to give any saline solution intravenously, and the patient was given the undiluted material, in the amount of 4 cc of Connaught heparin every three hours. The clotting time was frequently over an hour,

returning to 15 minutes or below in the three-hour period. This method is of value in the last few days of any course of heparin treatment, when it is advisable to have the patient get out of bed and walk without being encumbered by the intravenous apparatus.

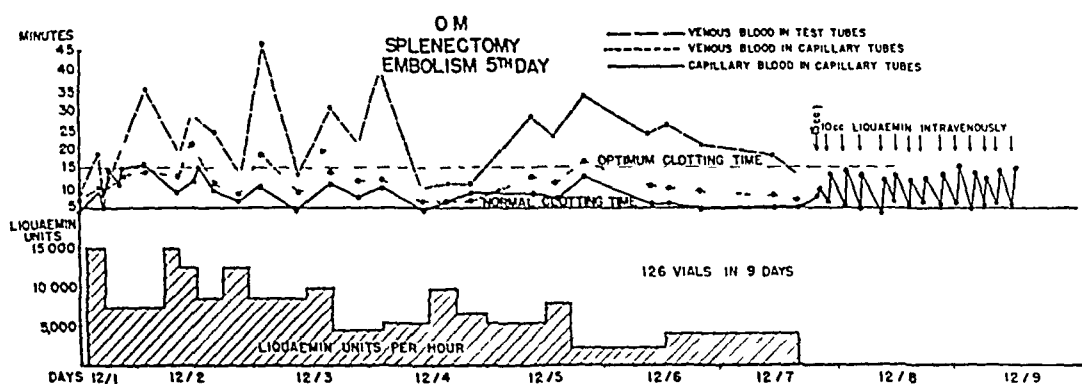


CHART 3—Chart of patient treated with Liqueamin with parallel clotting time determinations by three methods

Chart 3 illustrates one of the problems in heparin treatment, namely, the problem of clotting time methods. This is the chart of a patient who was treated with Liqueamin for a period of eight days. During the time when he was receiving the material by continuous intravenous drip, the clotting time was taken at intervals by three methods, namely, venous blood in test tubes, venous blood in capillary tubes, and capillary blood in capillary tubes. It can be seen that the clotting time as measured by the test tube technic was easily maintained at 15 minutes or above by the administration of small amounts of Liqueamin. However, considerably larger quantities would have been necessary to elevate the clotting time to 15 minutes as measured with capillary blood in capillary tubes. Venous blood in capillary tubes occupied an intermediate position. Many of the reports on heparin treatment are not clear on the matter of the clotting time method. In their original directions for heparin treatment, Murray and Best⁵ advised that the clotting time be elevated to 15 minutes as measured by the capillary tube method. Recently, Murray⁶ states that they are using venous blood in a 1 cc test tube, with a glass bead for an indicator. The directions accompanying the Liqueamin preparation suggest the use of the Lee and White method, in which venous blood is placed in several test tubes, which are inverted until clotting occurs, the clotting time in the fifth tube being taken as the reading. The determinations on Chart 3 were made with two test tubes. Obviously, reports on heparin treatment should state clearly the clotting time method used, if evaluations of the potency *in vivo* are to be made. At the present time, no one is willing to state what is the actual optimum clotting time to prevent thrombosis. The expense of heparin is such that one wants to use the least amount that will produce the desired effect. The case report which follows, taken alone, would cause one to try to maintain a clotting time of at least 15 minutes by the *capillary tube* method.

Case 1—The patient was an obese woman, age 43. She had drainage of an appendiceal abscess of 11 days duration on April 24, 1940. The postoperative course was stormy, with distention being a troublesome complication. Thus, many factors favoring embolism were present: namely, several weeks of recumbency in bed, infection, obesity, and increased intra-abdominal pressure from distention to retard back-flow from the veins of the legs. On May 25, 1940, one month after operation, and after orders had been left for her to get up the next day, she had a sudden attack of epigastric pain, sweating and shortness of breath. The diagnosis of pulmonary embolus was obvious, and heparin was begun. Large amounts of heparin were necessary to keep the clotting time near 15 minutes (Chart 4). The condition of the patient improved rapidly and heparin was to be discontinued on June 2, 1940, after one week of treatment. However, at 3:45 A.M. on this day, she awoke with dyspnea and a hacking cough which was productive of blood-streaked sputum. The condition of the patient grew steadily worse, there was marked air hunger and the skin was cold and moist. She was treated with oxygen, papaverine, morphine, and increased amounts of heparin, but she expired about 24 hours after the onset of the episode. Postmortem was refused, although it was sought with great diligence. From clinical examination, death appeared to be due to a second massive pulmonary embolism. However, acute heart failure could not be entirely ruled out.

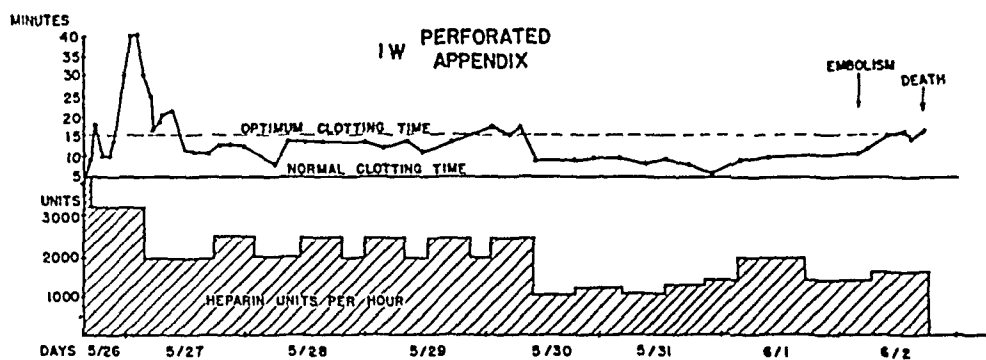


CHART 4—Heparin chart of patient who apparently had a second pulmonary embolism in the midst of heparin therapy

Fortunately, an accurate record of the amount of heparin given and the clotting times had been kept. This record showed that for about two days, the clotting time was ten minutes, and on one occasion it got as low as six minutes. Did a clot form during this brief period? Did a piece break off an old thrombus which had been waving in a large vessel for more than a week? Regrettably, the answer in this particular case can never be known. More information was obtained regarding the second fatality during heparin administration, because an autopsy was obtained.

Case 2—The patient was a man, age 69, who was admitted to the hospital on the Medical Service of Dr. Robert Durham. The provisional diagnosis was arteriosclerotic heart disease with fibrillation. He had two pulmonary embolisms, thought to have come from the right auricle, although the presence of femoral phlebitis was discovered later. He had marked dyspnea, and was heparinized as a last resort. He expired in one week, with signs of cardiac failure. Autopsy showed huge infarcts of the lungs, which were thought to be at least one week old. The cardiac muscle showed gross evidence of degeneration. No hemorrhagic manifestations were discernible.

The complication of hemorrhage has not been prominent in the previous reports. In 315 cases reported by Murray and Best,⁷ there were four instances

of hematoma formation in the wound, with the result that heparinization was stopped. Priestly, Essex and Barker⁴ noted only transient hematuria a few times in their 45 cases.

In this series, there was hemorrhage from the operative wound four times. Two patients bled from wounds in the popliteal space following embolectomy. Fortunately, the hemorrhage did not begin until four days had elapsed in each case, and the arteries remained patent, even though the heparin was discontinued. The third patient had a rather extensive dissection of the abdominal wall for the excision of a draining sinus. Three days later, he had pain in the chest suggestive of infarction and the next day heparin treatment was begun by the intermittent method, on account of the presence of cardiovascular insufficiency. Four cubic centimeters of Connaught heparin was given every three hours, and the clotting time rose to 20–30 minutes after each injection, the maximum being 46 minutes on one occasion. An hematoma developed on the second day, and the heparin was discontinued, inasmuch as sputum studies indicated that the pain in the chest was due to bronchopneumonia rather than embolism. The fourth patient had pain in the chest on the twelfth day following hysterectomy. Heparin was started, but was given in abnormally large amounts for several hours, with the result that the clotting time was 65 and 75 minutes on two occasions. The patient began to bleed from the vagina after 24 hours of treatment, and this was controlled with some difficulty by stopping the heparin and packing the vagina. One transfusion was given. Recovery was rapid.

There was one case of concealed hemorrhage. A very obese woman, age 42, had a spinal fusion. During the third week of convalescence, she had several small pulmonary embolisms. Heparin was begun, by the use of a continuous intravenous cannula placed in a vein on the medial side of the left ankle. The right leg is usually used for this procedure, on account of the propensity of the left for phlebitis, but in this case a bone graft had been removed from the right leg, so the left was chosen. The clotting time was maintained at the optimum level by giving 1,000 units of heparin per hour (Chart 5). On the third day of treatment, the patient complained of severe

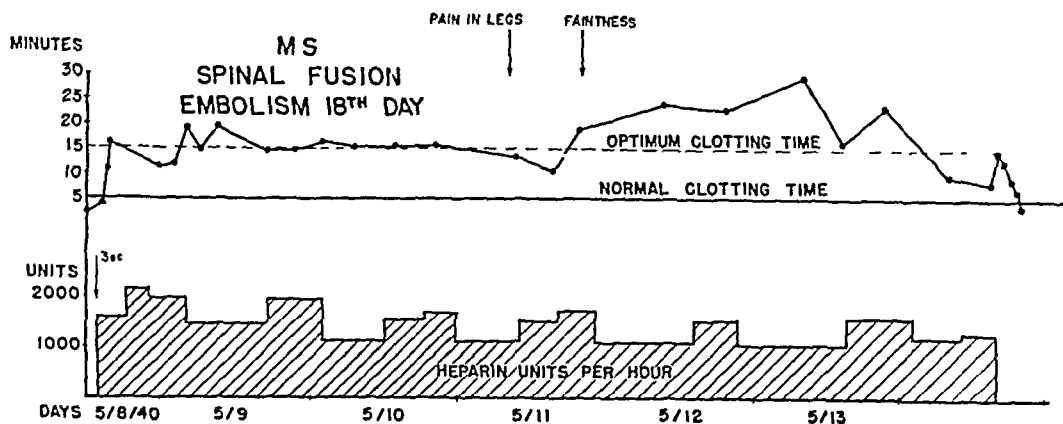


CHART 5—Heparin chart of patient who developed a massive hematoma in the thigh (Fig. 1)

pain in the region of the femoral vessels of the left leg. The leg was repeatedly examined, and no cause for the pain could be found. Later, she complained of feeling faint. The true state of affairs was not recognized until three days later, when bulging in the left thigh was noted (Fig. 1). The

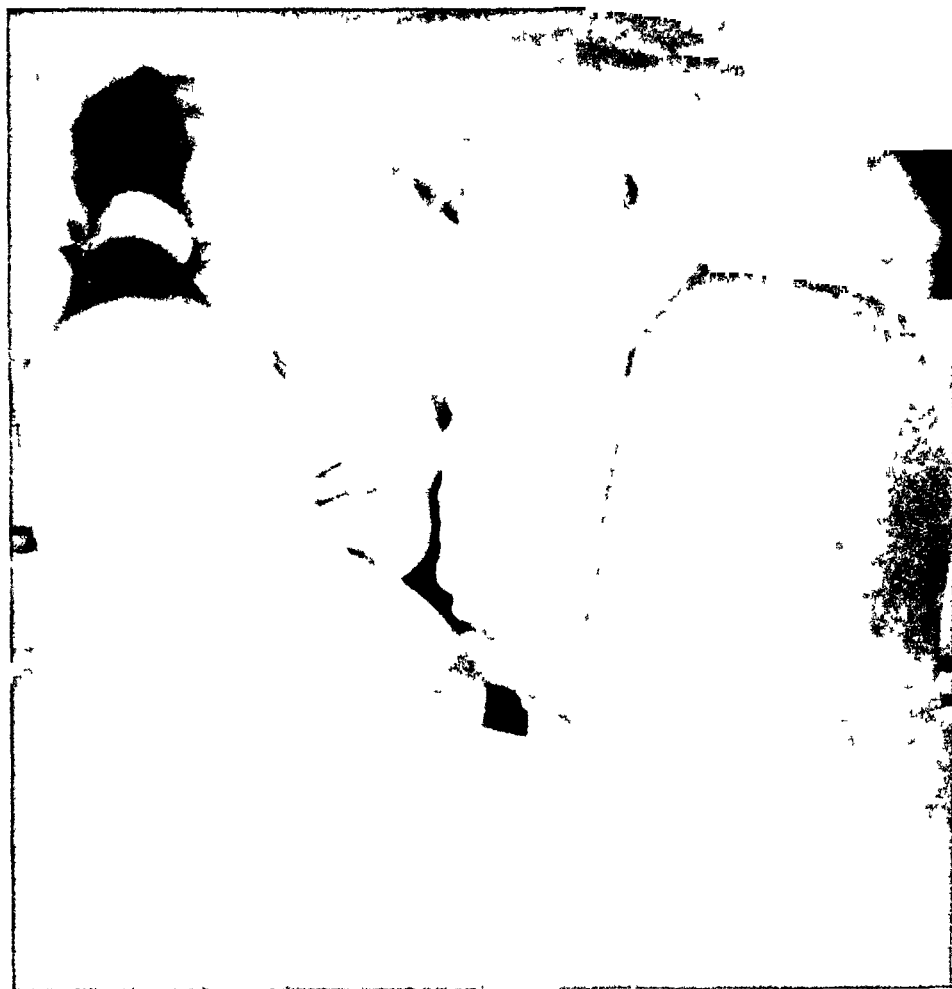


FIG. 1.—Photograph of legs of the patient who developed a huge hematoma in the left leg on the third day of heparin administration.

hemoglobin determination at this time showed 5 Gm., or 33 per cent. It was obvious that the swelling represented a massive hematoma which had come from an unknown source in the leg. It is of interest to note that the vitamin C on the patient this day was 0.20 mg., which is about scurvy level, and there was evidence of capillary fragility by the tourniquet test. Apparently the combination of the two hemorrhagic tendencies resulted in the subcutaneous bleeding.

COMMENT—It has not been my intention to paint a dark picture for heparin therapy. I have mentioned the complications, having little to say about the other cases who comprise the majority of the series, who had uninterrupted recoveries after having had one, two, and even three previous

pulmonary infarcts. Heparin has a place in the treatment of thrombosis. Its value in embolectomy and other kinds of blood vessel surgery is even greater. However, those who use heparin should keep in mind such reports as that of Potts,⁹ who carried 518 patients through various operative procedures with no clinically recognizable evidence of thrombosis or embolism, by simply making them carry out a simple exercise in bed.¹ Still more puzzling is the report of Reed,¹⁰ who stated that he had deliberately *reduced* the clotting time in a series of operative cases, by the administration of adrenal cortical extract. He had had no embolism or thrombosis in over 200 cases.¹

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PECTIN SOLUTION AS A BLOOD SUBSTITUTE

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The present war has reemphasized the urgent need for blood and blood plasma in the fluid or desiccated state which may be used to combat shock and hemorrhage. In line with other defense work, the collection of desiccated plasma for our own armed forces has been undertaken by the American Red Cross under the supervision of the National Research Council. The present specifications covering the preparation of this material require the desiccation from the frozen state. With the largest units desiccating from the frozen state, such as used by Best at the Banting Institute, only 1,000 units of 250 cc each can be produced per week. Even with our method¹ of desiccation from cellophane cylinders with a production of 1,200 units of 250 cc per week, the matter of obtaining such large quantities of human blood remains a great problem. From the standpoint of production alone, to say nothing of cost, transportation, storage, and application, it seems obvious that some other substances which may be used as substitutes or supplements for blood and blood plasma must be found.

The widespread and successful use of blood plasma and blood serum in shock and hemorrhage has demonstrated most convincingly that the primary need in such emergencies is to replenish the volume of circulating fluid with a fluid which has identical or similar physical characteristics rather than new red blood cells. The red blood cells may in fact be distinctly contraindicated in shock without hemorrhage.²

In a recent article, Taylor and Waters³ outline the requirements of a transfusion fluid which will restore and maintain the volume of circulating fluid as follows: "(a) The molecule of the dissolved substance must be of such a size that the fluid will not leave the vessels too freely. (b) The solution must exert an osmotic pressure and possess a viscosity approaching as closely as possible that of whole blood, these qualifications depend upon molecular size and shape. (c) It should be as nearly as possible isotonic with the contents of erythrocytes. (d) It must of course, be nonantigenic and innocuous in every respect. In addition, it should be readily available, preferably cheap, and capable of being quickly and easily prepared for intravenous administration."

To meet these requirements, Taylor and Waters propose the use of isinglass (fish gelatin) especially prepared from fish swimming-bladders. Some difficulty in purification has been encountered, but in animal experiments it seems to answer the purpose and only a few reactions were encountered. It

is held superior to ordinary gelatin which does have definite antigenic properties

The second colloidal material which has been widely used as a blood substitute is gum acacia. Its use was suggested by Bayliss,¹ in 1916 under the title "Methods of Raising a Low Arterial Pressure," and supported by Rous and Wilson,² in 1918 under the title "Fluid Substitutes for Transfusion after Hemorrhage." The favorable results reported by Bayliss and Rous and Wilson were confirmed by some investigators and objections were brought out by others. Hanzlik and Karsner³ in 1922 in a study of various colloids state regarding acacia "It injures the circulatory and respiratory systems as indicated by the presence of anaphylactoid symptoms, pulmonary distention, congestion and hemorrhage together with cardiac dilatation. Thrombi in the pulmonary vessels occurred after the injection of acacia in therapeutic doses and concentrations." Maytum and Magath⁴ in 1932 confirmed the fact that even the best solutions might be antigenic. "Solution of acacia is a mild antigen. There is no danger in the first dose of acacia but subsequent doses should be given cautiously because of the possibility of anaphylactic reactions." Yule and Knutti⁵ in 1939 showed that the livers of dogs injected weekly with acacia may increase five to six times in weight and contain 8 to 10 per cent of acacia by weight. Further it was found that acacia persisted as long as 144 days in the blood and that the plasma proteins were depressed to very low levels particularly the fibrinogen fraction which remained low for several months.

Andersch and Gibson⁶ report that 30 per cent of the injected acacia was found in the livers of dogs and 43 per cent of 46 Gm injected was found in the liver of a nephrosis patient.

Jackson and Frayser¹⁰ in 1939 found that "the fibrinogen may become very low and cause considerable delay in clotting and prolongation of bleeding if large amounts of acacia are given."

Thus it is apparent that while acacia satisfies the first three requirements, it fails in the fourth since it is antigenic and is stored in the liver, interfering with liver function.

The difficulties encountered in the intravenous use of acacia have been detailed because it is obvious that any new colloidal solution proposed for intravenous use in shock and hemorrhage must eliminate most or all of these disadvantages, if it is to be a truly acceptable substitute for whole blood or blood plasma.

Pectin is a substance very familiar to the profession but its therapeutic application has been confined to the skin and intestinal tract. It may be described, according to Gortner¹¹ as a colloidal carbohydrate of high molecular weight and rather complex composition. On hydrolysis it is said to produce galacturonic acid, galactose, arabinose, xylose, methanol, and acetic acid. Protopectin is the mother substance of the pectins and both are found in the plant cell walls where they are probably combined with cellulose. Protopectin may be hydrolyzed free from the cellulose and converted into

soluble pectin, usually by treatment with 0.5 per cent ammonium oxalate at 70 to 90° C. or by heating with dilute acids. The pectin resulting from either form of hydrolysis is of high molecular weight, disperses in water to a viscous colloid solution and is readily precipitated from this solution by alcohol.

Myers and Baker¹² believe that lemon pectin is monoarabinomono-galactodiacetylheptamethoxylactagalacturonic acid, giving a formula of $C_{70}H_{95}O_{78}$ with a molecular weight of 1866. Bonner¹³ suggests a cellulose-like chain formula. Henglein and Schneider¹⁴ nitrated pectin and found the resulting material with the physical characteristics similar to nitrocellulose.

Source and Preparation of Pectin for Intravenous Use—Pectin in the dry powder form obtained from two manufacturers was used in this work. One brand bore the label "pure grapefruit pectin" and the other "pectin-technical grade." The former designated as Brand I is a light brown granular material which is sufficiently soluble in warm double distilled water to readily make a 1 per cent solution. It is filtered through No. 1 Whatman papers. This solution is slightly opalescent and has a pH of 3.05. Its viscosity is 10.15 at 38° C. and its osmotic pressure is 50 Mm. of mercury. Since the viscosity of whole blood is about six and the osmotic pressure of plasma is 25 to 30 Mm. of mercury, the 1 per cent solution of Brand I is diluted with equal quantities of 1.8 per cent NaCl or double strength Ringer's solution then phosphate buffers are added in sufficient quantity to bring the pH to 6.5. The pectin obtained from the second manufacturer, Brand II, is a white powder which contains 35 per cent glucose. Because of the difficulty in separating this glucose, the material was used in a 1 per cent solution made up in double distilled water. It is filtered through No. 1 Whatman papers. This solution has a viscosity of 3.5 and an osmotic pressure of 22 Mm. of mercury. Eight-tenths of 1 per cent NaCl and phosphate buffers are added to bring the pH to 6.5. Both solutions are sterilized under steam pressure of 15 pounds for 20 minutes. After sterilization the solutions are still slightly opalescent and is further buffered to pH 7.2. As with other colloidal solutions, every lot does not turn out alike, therefore it is necessary to test each lot against citrated blood and suspensions of red blood cells examining for hemolysis, rapid sedimentation, and precipitation of fibrin. If any of these occur the solution must be rejected.

Experimental—No evidence has been found in the literature to indicate that pectin is an antigenic substance, but since it has not been used intravenously as a therapeutic agent, it seemed desirable to determine whether or not it was antigenic or whether it would produce so-called anaphylactoid symptoms. To this end three guinea-pigs were injected intravenously with 1 cc., 1.5 cc. and 2 cc. of the 1 per cent buffered pectin solution and at the end of 14 days with the same amounts intravenously. No reaction occurred.

Twelve rabbits of six and eight pounds each were given 1 per cent buffered pectin solutions intravenously in amounts ranging from 50 to 100 cc. These doses were repeated after one week and after two weeks, but no immediate

or delayed reaction occurred. Three dogs, as indicated in Table I, were injected four times over a 26-day period with 1 per cent buffered pectin solution in doses ranging from 300 to 350 cc, each time without anaphylactic symptoms.

TABLE I
LIVER FUNCTION FOLLOWING PECTIN INJECTION

Dog and Weight	Date 1941	Gm Pectin per Kg	B S P Liver Function Test		
			5'	10'	20'
P 60					
15.5 Kg	6/12	0.19			
	6/17	0.22			
	6/18		50%	30%	20%
	6/21		25%	15%	neg.
	6/23	0.19			
	7/7	0.25			
	7/7 (4 hrs.)		10%	20%	10%
	7/8 (24 hrs.)		10%	20%	7%
7/11		35%	10%	neg.	
P 70					
11.4 Kg	6/12	0.26			
	6/17	0.26			
	6/18		45%	20%	15%
	6/21		35%	10%	neg.
	6/23	0.26			
	7/7	0.35			
	7/7 (4 hrs.)		55%	25%	15%
	7/8 (24 hrs.)		60%	25%	10%
7/11		35%	5%	neg.	
P 80					
17.7 Kg	6/12	0.17			
	6/17	0.17			
	6/18		45%	15%	5%
	6/21		25%	10%	neg.
	6/23	0.17			
	7/7	0.23			
	7/7 (4 hrs.)		50%	35%	20%
	7/8 (24 hrs.)		30%	15%	10%
7/11		25%	5%	trace	

The disposition of pectin in the body after it is injected intravenously is of primary importance, since one of the principle difficulties with acacia is its retention in the blood and tissues, especially in the liver. Pectin is also taken up by the liver, especially if a single large dose is administered. In six to eight pound rabbits receiving 100 to 150 cc of the 1 per cent buffered pectin solution at one time and sacrificed three hours later, there was no marked gross enlargement of the liver, but microscopically the hepatic cells appeared swollen and filled with small clear granules. A dog of 16 Kg receiving 425 cc of 1 per cent buffered pectin solution, and autopsied 14 hours later, failed to show either gross or microscopic evidence of liver retention. As seen in Table I, the fractional bromsulphthalein test of liver function after the injection of large amounts of pectin solution showed a temporary blocking which

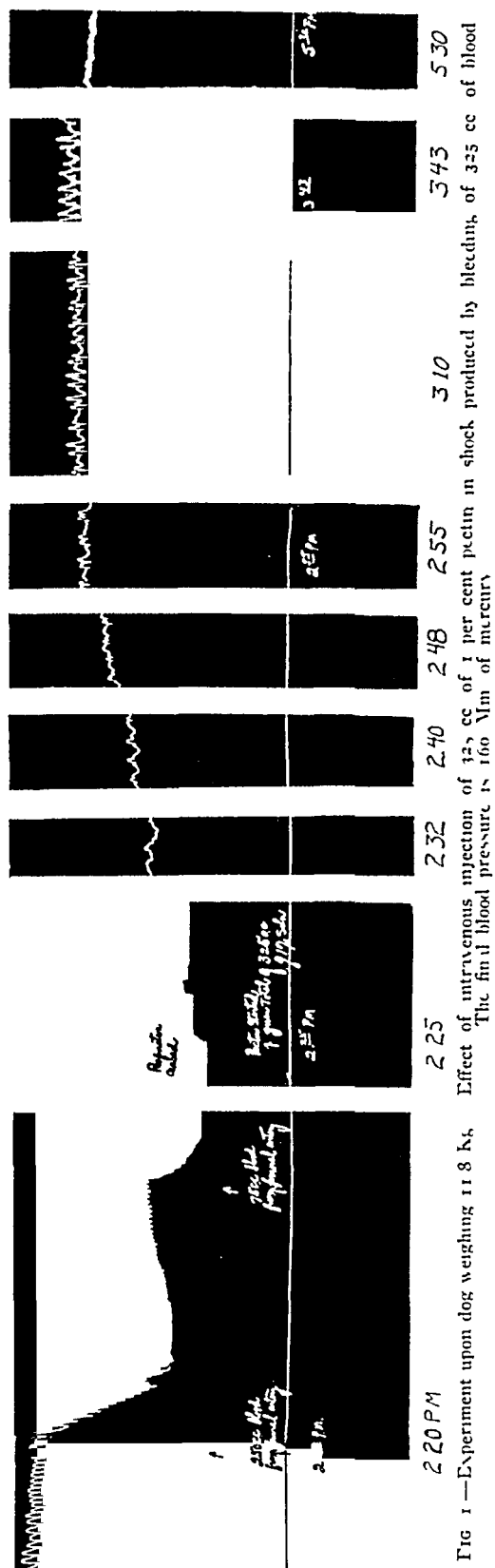


FIG 1.—Experiment upon dog weighing 11.8 kg.

PECTIN SOLUTION AS A BLOOD SUBSTITUTE

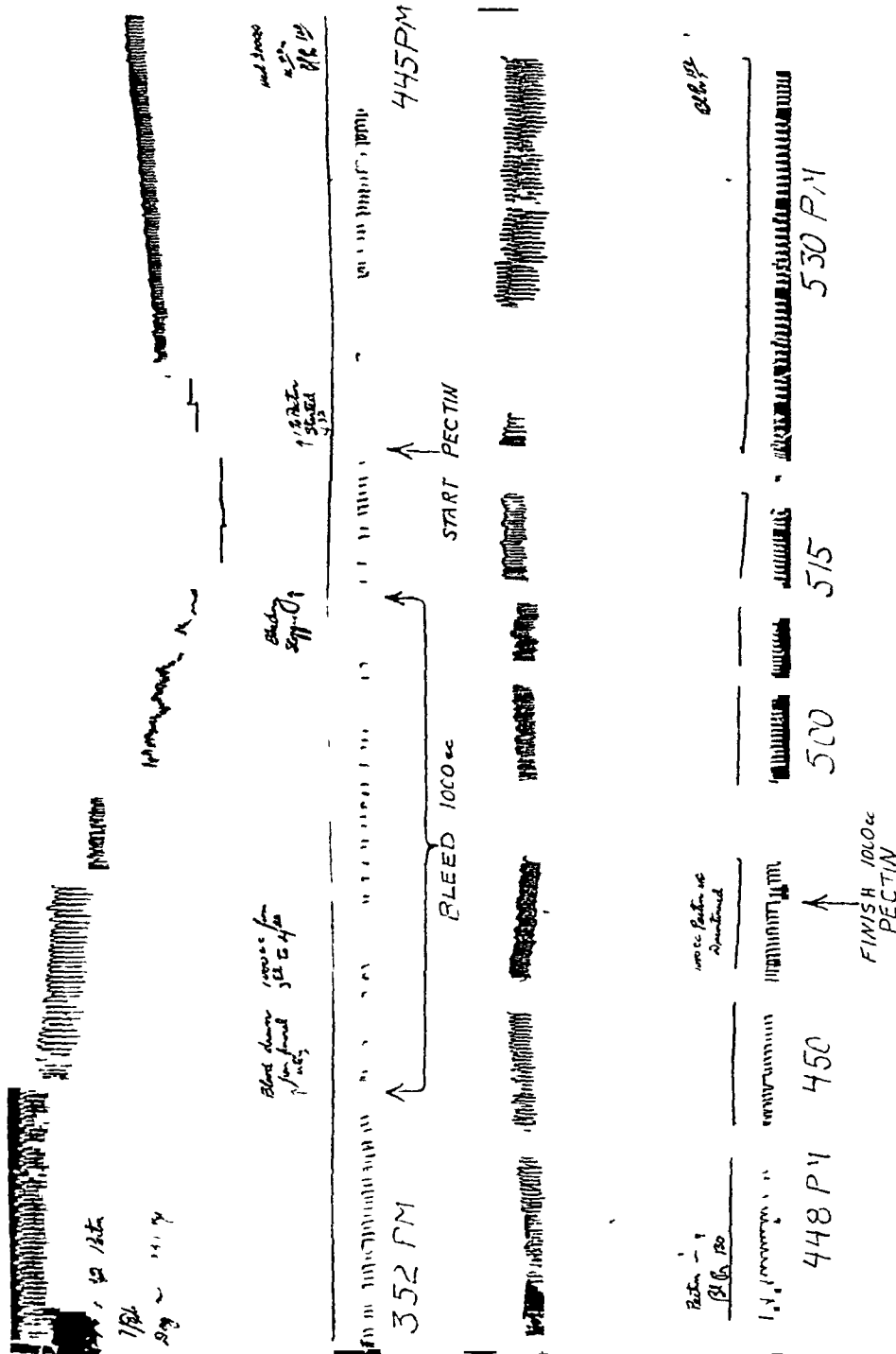


Fig 2 —Experiment upon dog weighing 23.1 Kg. Effect of intravenous injection of 1,000 cc of 1 per cent pectin in shock produced by bleeding of 1,000 cc of blood. The final blood pressure is 160 mm of mercury

cleared rapidly and showed no tendency toward a cumulative storage or blockage even with four large doses in a 26-day period

The temporary character of the body's retention of pectin is demonstrated further by its excretion in the urine. It is excreted unchanged, as demonstrated by precipitation when equal quantities of urine and absolute alcohol or urine and acetone are mixed. In either case the pectin is thrown down as a white flocculant precipitate. A rough quantitative estimation of the amounts may be made by comparing with a known solution which has been precipitated in the same manner. The excretion of pectin is small for the first eight to 12 hours after the injection but reaches the maximum within 24 hours, and within 48 to 72 hours the major portion of the pectin is eliminated.

Considering the source, method of production, and chemical nature of pectin, there is nothing to suggest that it would be toxic for the body or its component units. Further, pectin has been used extensively in man as a local application to wounds and in the gastro-intestinal tract without toxicity. With solutions prepared and tested as described, there have been no indications of toxicity in either man or animal. Pectin solutions which are not properly adjusted as to the pH and which have a viscosity above five are poorly tolerated in animals and must be guarded against in clinical work.

A series of 12 experiments were performed upon animals in order to assay the value of pectin for blood replacement in shock following (a) hemorrhage, and (b) experimental bile peritonitis, and observe its effect on (c) blood concentration and (d) as a replacement for plasma in plasmapheresis.

(a) In four animals, shock was produced by *hemorrhage*. As seen from Table II, the amounts of blood removed, while considerable, were not sufficient to alone cause death in all instances, but the effects of pectin in restoring blood pressure are quite striking. As seen from Figures 1 and 2, the restored level of blood pressure was well maintained after the administration of pectin solution intravenously.

TABLE II
THE USE OF PECTIN IN SHOCK FOLLOWING EXPERIMENTAL HEMORRHAGE

Experiment No	Dog, Wt Kg	Initial Blood Pressure Mm Hg	Bled cc	Blood Pressure After Bleeding Mm Hg	Inject cc 1% Pectin Intra venously	Final Blood Pressure Mm Hg	Result
1	11.8	110	325	80	320	155	Died. Lung abscesses found at necropsy
2	12.2	150	375	50	475*	130	Recovered
3	13.6	138	500	90	500†	110	Recovered
4	23.1	180	1,000	80	1,000	160	Recovered

* Plus 150 cc whole blood

† One half per cent pectin used in this experiment

(b) Five animals with *bile peritonitis* were treated with pectin. The bile peritonitis was produced by the intraperitoneal injection of sterile 10 per cent solution of Armour's repurified bile salts. A marked hemoconcentration as

evidenced by a rise in the hematocrit resulted. This rise and the associated marked fall in arterial blood pressure are shown for a typical experiment in Table III. Three animals in this stage were then treated with intravenous

TABLE III

THE USE OF PECTIN IN SHOCK FROM BILE PERITONITIS

Typical Experiment (In the other two experiments the animals lived ten plus and 22 hours after injection of the bile salts intraperitoneally.)

Dog weight—11.8 Kg
Initial readings: Blood pressure—140 Mm Hg, hematocrit—46%
Inject 89 cc 10% bile salt solution intraperitoneally
Time interval—3½ hours
Subsequent readings: Blood pressure—60 Mm Hg, hematocrit—69%
Inject 230 cc 10% pectin intravenously
Later readings: Blood pressure—128 Mm Hg, hematocrit—58%
Death six hours after intraperitoneal bile injection

pectin injections as shown in Figures 3 and 4, and a temporary improvement in hematocrit reading and blood pressure level occurred. These experiments were made to observe this effect rather than to attempt a permanent cure since it is well known that in instances of bile peritonitis of this severity even plasma will not prevent death.¹⁵

TABLE IV

PECTIN PLASMAPHERESIS EXPERIMENT JULY 5, 1941

Dog Weight 11.8 Kg Nembutal Anesthesia

Time P M	Hema- to-crit	Observation			Remove Cc			Administer Cc	
		Gm /100 Cc			Whole Blood	Cells	Plasma	Cells	1% Pectin
		Albumin	Globulin	Total					
4 12	41	3 39	1 52	4 91					
4 18					200	105	95		
4 45-5 00								105	130
5 02	45	2 09	1 73	3 82					
5 05					175	95	80		
5 11-5 31								95	130
5 35	45	1 76	1 84	3 60					
5 37					175	105	70		
5 38-6 03								105	100
6 07	50	2 09	1 09	3 18					
6 08					175	105	70		
6 09-6 31								105	100
6 32	52	1 97	0 87	2 84					
Totals					725	410	325	410	460

Two other animals were given pectin before the production of bile peritonitis with no demonstrable prolongation of life over that observed in similar control experiments.

(c) In one experiment, pectin solution was rapidly injected to see if it could cause a blood *concentration* or *dilution*. A rapid *dilution* was observed, unlike the paradoxical blood concentration following concentrated plasma injections observed by Harkins, Boals and Brush.¹⁶ In this same experiment, frequent determinations of the blood clotting time were made with no demonstrable prolongation being observed.

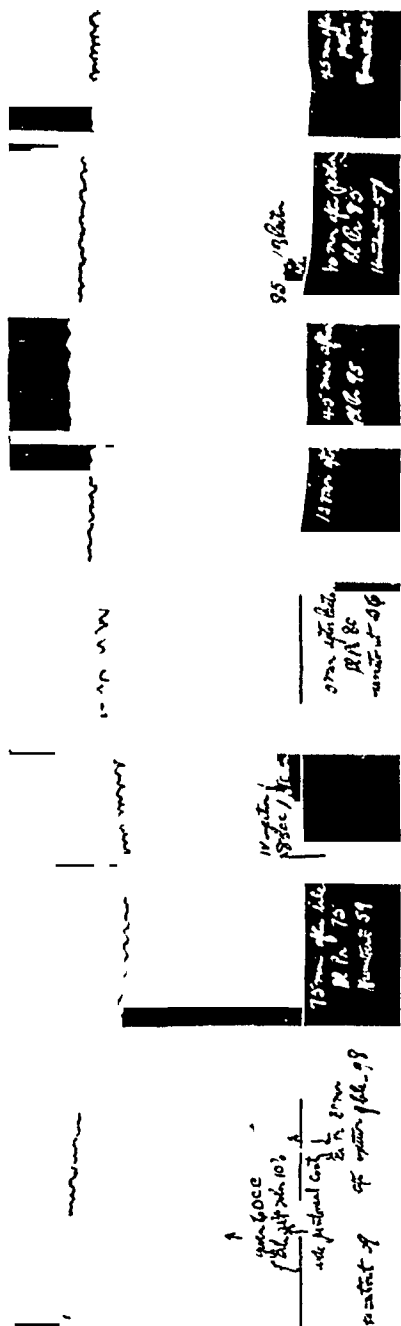


FIG. 3—Effect of intravenous injection of 255 cc of 1 per cent pectin in shock produced by the intraperitoneal injection of 60 cc of 10 per cent sterile bile salt solution. The hematoctrit rose from 39 to 59 before pectin was given and then fell to 56. It later rose to 62. The last blood pressure shown on the chart 15 minutes after pectin administration is 136 mm of mercury. The animal died 22 hours after production of the peritonitis.

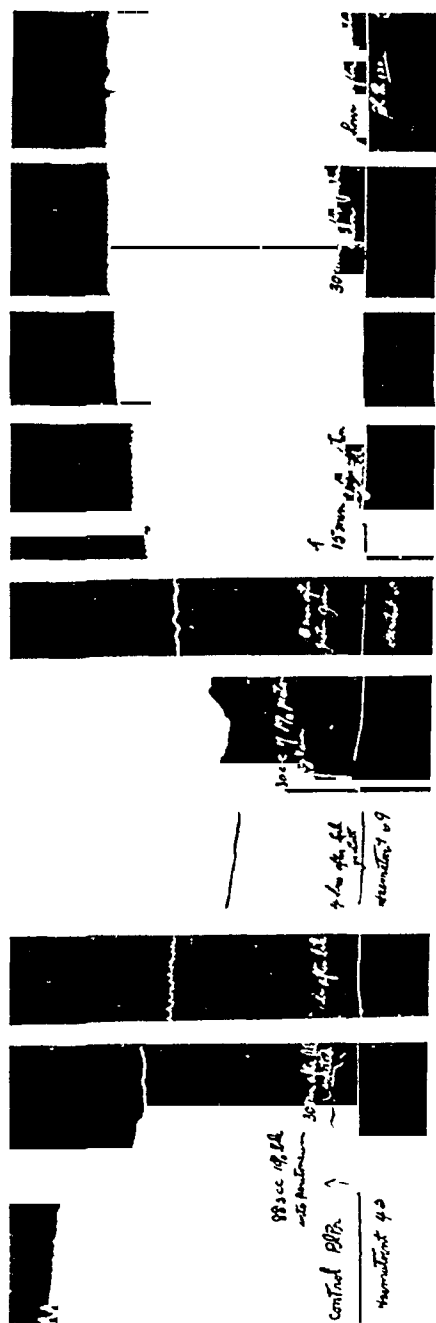


FIG. 4—Effect of intravenous injection of 230 cc of 1 per cent pectin in shock produced by the intraperitoneal injection of 89 cc of 10 per cent sterile bile salt solution. Accompanying hematoctrit readings are shown in Table II. The last blood pressure shown on the chart one hour after pectin administration is 162 mm of mercury. The animal died 48 hours after production of the peritonitis.

(d) In two dogs, *plasmapheresis* was done. After centrifuging withdrawn samples of blood, the plasma was discarded and replaced by an equal or slightly greater amount of 1 per cent pectin solution. The cell-pectin mixture

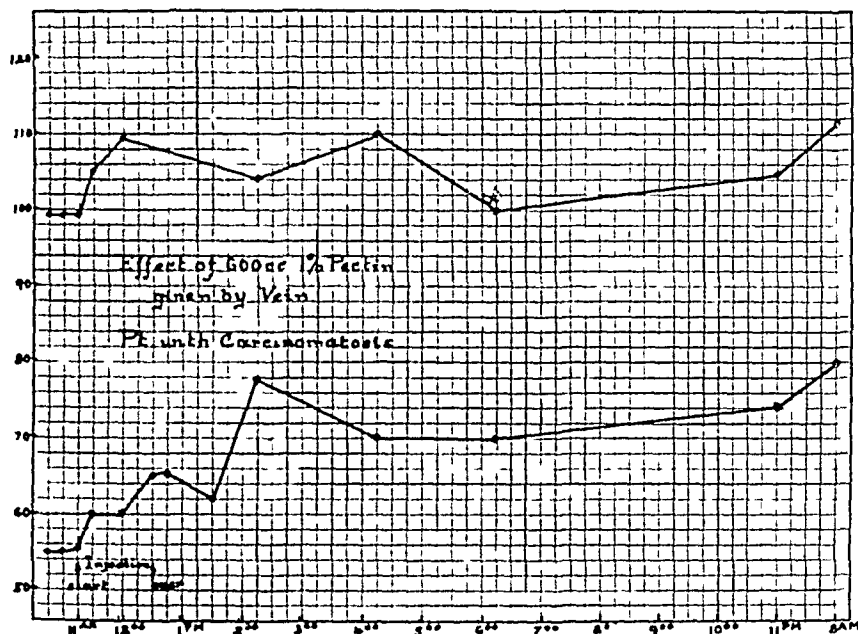


FIG 5—Case 1 Effect of intravenous injection of 600 cc of 1 per cent pectin in patient B. M.

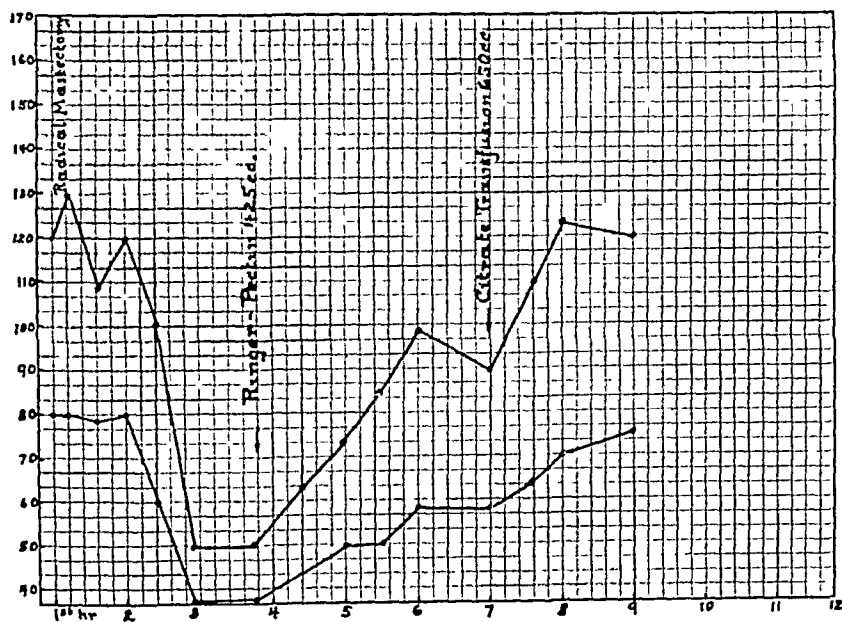


FIG 6—Case 2 M. W. No 16863. A female, white age 42. Weight 130 lbs. Lump in right breast for three months. Admission blood pressure 140/85. Operation July 1, 1941—Radical mastectomy with skin graft from right thigh (Preoperative hemoglobin 12.5 Gms). Anesthetic ethylene. Received 450 cc of 1 per cent pectin solution intravenously after returning from the operating room in shock. Condition improved and the systolic blood pressure rose from 50 to 93.

was then immediately reinserted in the animal. This procedure was repeated a total of four times in one experiment and five times in the other, withdrawing samples of about 200 cc of blood each time. In one experiment, the hematocrit did not vary at all, while in the other, it increased somewhat as seen in Table IV. The marked decrease in total plasma proteins following pectin replacement in this animal is noteworthy.

CLINICAL OBSERVATION

Case 1—Pectin Injection in Patient Not in Shock. B. W., a female, age 54, had a palliative operation for carcinoma of the right breast October 8, 1940. She returned to the hospital, June 30, 1941, with multiple metastases. An intravenous injection of 600 cc of 1 per cent pectin was given July 3, 1941. The chief effects were a slight feeling of well-being and an elevation of blood pressure from a mild hypotensive to a more normal level as shown in Figure 5. A slight chill with a transient temperature elevation to 101.4°F might well be attributed to a coincident bromsulphthalein test. Furthermore, the patient had a daily diurnal rise to 99.0°F each day before the pectin administration. Liver function and renal function tests were performed before and after the giving of pectin. On July 2, 1941, the bromsulphthalein retention was ten minutes—10 per cent, 20 minutes—0, and 30 minutes—0, and on July 4, the day after pectin injection, the test was exactly the same. A phenolsulphonphthalein test on July 2 showed 65 per cent excretion in one hour and 15 per cent in the second hour for a total of 80 per cent. On July 4, the day after pectin injection, the readings were identical. Hematocrit readings were constant (decrease from 38 to 37) and the clotting time also showed no appreciable change. Blood protein analyses, in grams per cent, were as follows:

	Albumin	Globulin	Fibrinogen	Total
July 2, 1941 (before pectin)	4.04	2.27	0.40	6.71
July 3, 1941 (just after pectin)	1.98	1.17	0.43	6.58

The clinical use of pectin in shock is illustrated in Figures 6, 7 and 8.

Discussion.—The use of pectin as the colloid base for a blood substitute is logical because it is one of the most hydrophilic colloids, only 0.5 Gm. of pure material per 100 cc of solution being required to make a solution with a viscosity and osmotic pressure near that of whole blood. Thus 14 times more acacia, gelatin or isinglass, gram for gram, is required to make a suitable intravenous solution, than is required with pectin.

The source—citrous fruits—and the method of production—chemical and electrolytic extraction, give an abundant supply, free of gross bacteriologic contamination, at nominal cost.

Preparation and sterilization of the solution is readily accomplished, but certain essentials must be observed, i.e., neutralization, addition of electrolytes and testing for (a) viscosity, (b) hemolysis of red blood cells, (c) sedimentation of red blood cells, and (d) precipitation of fibrin.

The preliminary experimental work indicates that pectin is nonantigenic and nontoxic. It is retained in the body for a short period and then eliminated rapidly. There appears to be no cumulative effect in using the solutions described. Liver function as measured by the fractional bromsulphthalein test, and fibrinogen shows slight depression only with massive doses. In the 12 experiments on shock and hemorrhage prompt and adequate response as

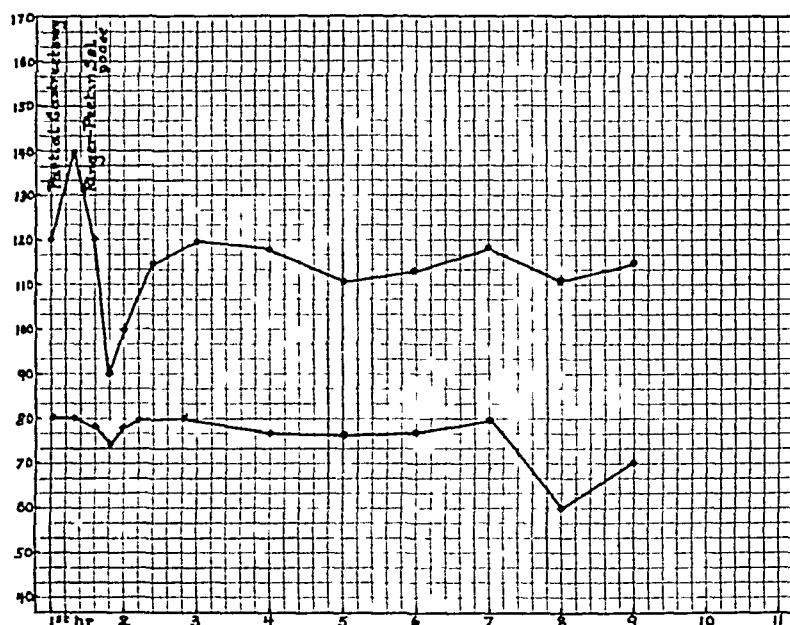


FIG 7—Case 3 C V No 271727 White, female age 56 Gastric ulcer with continuous symptoms for five years Height 5'2", weight 134½ lbs Operation July 3 1941—Partial gastric resection Preoperative blood pressure 88/64 hemoglobin 13.5 Gms Received 950 cc of 1 per cent pectin during the operation rather than the customary transfusion of whole blood The blood pressure was maintained well above the preoperative level Post operative course was uneventful

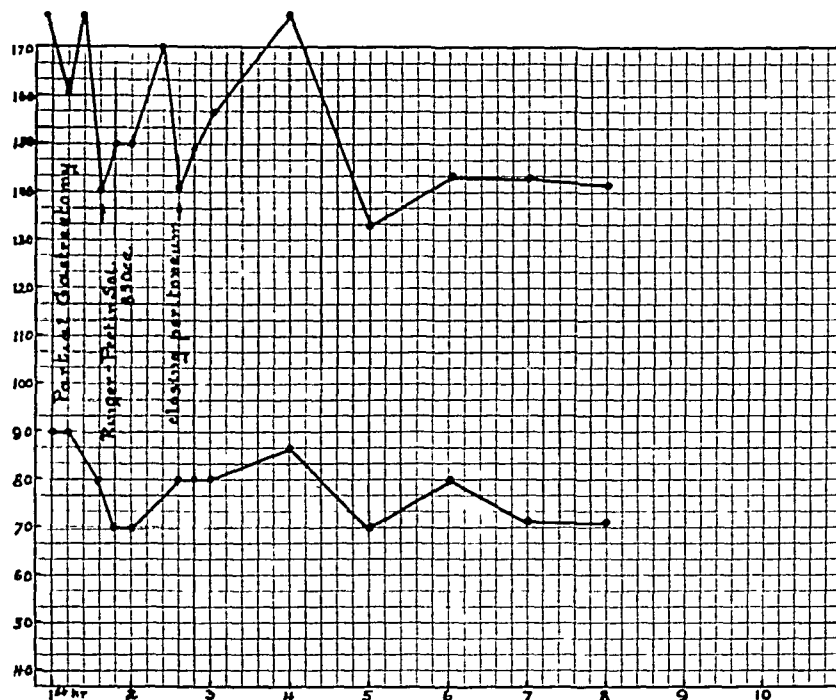


FIG 8—Case 4 J M No 186791 White male age 66 Duodenal ulcer for past 15 years 5'6" tall weight 140 lbs Present studies show marked gastric retention and gallstones On 7/3/41 had cholecystectomy, appendectomy and posterior gastroenterostomy Admission blood pressure 120/70 Postoperative course uneventful Anesthetic cyclopropane and ethylene (preoperative Hb 15 Gm) Received 900 cc of 1% pectin during the course of the operation instead of the usual blood transfusion Blood pressure levels were sustained at satisfactory levels

measured by blood pressure graphs and the general condition of the animals was obtained in all

The preliminary clinical application shows the patient (Case 1, Fig 5) not in shock, with a moderate elevation of blood pressure after 600 cc of 1 per cent buffered pectin solution. The bleeding time, coagulation time, and liver function were not altered. The mastectomy patient (Case 2, Fig 6) in shock received a small injection of 450 cc of the 1 per cent solution but the condition improved steadily over a three-hour period. The two patients receiving injections instead of the usual transfusions during partial gastrectomy operations (Cases 3 and 4, Figs 7 and 8) maintained satisfactory blood pressure levels throughout. Three additional operative cases and one normal individual have received pectin intravenously without reaction or untoward results. In the operative cases, especial attention was paid to the bleeding time in the tissues of the operative wound but no variation from normal could be observed.

SUMMARY

(1) The intravenous use of pectin solution as a blood substitute in shock is proposed.

(2) One-half per cent of pure pectin solution has about the same viscosity and osmotic pressure as whole blood.

(3) Pectin has a high molecular weight, is nonantigenic and nontoxic.

(4) The source, method of manufacture, and the ease of preparing and sterilizing stable buffered solutions make pectin readily available.

(5) Preliminary experimental and clinical application indicate that pectin solutions are valuable in the management of shock.

(6) There is temporary retention of pectin in the blood and in the liver but excretion of the unchanged material in the urine is rapid.

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CANCER OF THE LIP*

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PART I

CANCER OF THE LIP is the most frequent but not the most fatal malignant neoplasm of the oral cavity. Unlike other intra-oral cancers, it can always be diagnosed early, and, except when a lesion is neglected and permitted to progress to advanced and complicated stages, the treatment, if intelligently conceived, is less hazardous and less difficult, technically, than that of most other serious forms of malignant growth.

The present report is based upon an intensive analysis of 375 consecutive cases of lip cancer, all histologically proved, admitted during the seven-year period, 1928 to 1934, and includes all patients with cancer of the lip who applied to our clinic during that period, without exclusion of any because of an advanced stage of the disease. Of the entire group, 99 patients (26 per cent) had received previous treatment by one of the accepted methods (surgery, radium, roentgenotherapy, endothermy or combinations of them) and were admitted to our clinic with residual or recurrent disease. The treatment methods described are those which have been evolved at the Memorial Hospital during the past 25 years, beginning with the original radium technics of Janeway²⁶ and Quick.¹⁶

Definition—Properly speaking, cancer of the lip is a mucous membrane tumor both anatomically and clinically, and, therefore, the term should be limited to those lesions which arise in the vermilion border or in the mucocutaneous junction of the lips. Basal cell carcinomas (which never arise in mucous membrane) and all other growths which develop on the skin apart from the vermilion border of the lips should not be included in this classification, but should be grouped with other cancers of the skin of the face.

ETIOLOGY

General Incidence—According to the admission records of the Memorial Hospital, cancer of the lip comprises about 30 per cent of all malignant tumors of the oral cavity proper, about 20 per cent of all cancer of the upper respiratory and alimentary tracts, and about 4 per cent of all admissions for cancer. The latter figure is twice that reported by Widmann⁶⁴ (2 per cent) from the Philadelphia General Hospital, and by Stewart⁵⁶ from the Steiner

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Clinic According to statistics furnished us by the Bureau of Records of New York City (1937),¹ cancer of the lip, despite its relatively high incidence, causes only 0.3 per cent of all cancer deaths, or one-fourth as many as the equally frequent cancer of the tongue (1.2 per cent of all cancer deaths)

Age and Sex—In the series herein reported, the oldest patient was aged 88, the youngest aged 28, and the mean age for the entire group was 56 years. The average age as reported by other investigators varies between 52¹⁸ and 65.⁶⁵ The majority (67 per cent) of our cases occurred between the ages of 50 and 69, with about 40 per cent after the age of 60.

In our clinic, the disease is limited almost entirely to males (98 per cent in the present series). Other investigators^{21, 43, 55, 57, 41} have reported a female incidence ranging from 1 to 16 per cent. The reports from the Scandinavian countries^{1, 2} indicate that cancer of the lip is more common among women there than it is in this country. Ahlbom,¹ in commenting upon this relatively high female incidence, suggests that it may be due to mucous membrane changes associated with achlorhydric anemia and the Plummer-Vinson syndrome which are so common among women in Sweden.

Race—Cancer of the lip (like cancer of the skin) is more frequent in the white than in the colored race, probably for the reason that highly pigmented skins and mucous membranes are less subject to chronic irritation from physical sources (sunshine, weather, chemical irritants, etc.). In the present series, all were of the white race. It is obvious, however, that this comparative regional immunity to lip cancer does not extend to the rest of the oral cavity, for it is well known that the Negro is particularly subject to lingual and buccal cancer arising on the basis of chronic syphilis. While the records of the Memorial Hospital contain a few cases of lip cancer in mulattoes, so far as we know, none has occurred in a full-blooded Negro. Hall²⁴ does not state whether or not the three Negroes reported in his series were full-blooded. According to Brewer,⁷ the disease is not uncommon in Negro women who are pipe smokers.

Position of the Growth—The disease occurs almost exclusively on the lower lip (93 per cent). In the present series, only 6 per cent of the lesions occurred on the upper lip and about 1 per cent directly in one of the labial commissures. Some authors report much larger relative percentages of cancer of the upper lip, as for instance Forssell²³ 25 per cent, and Widmann⁶⁴ 10 per cent. Such figures are difficult to explain unless one assumes that these observers included basal cell carcinomas of the skin apart from the vermilion border of the upper lip, which we believe should properly be placed in the general group of skin cancers.

It may be of passing interest to note the percentage distribution of lip cancer as regards the right and left sides, excluding, of course, those growths arising directly in the midline. In the present series, 56 per cent occurred on the left. Simmons⁵⁵ found 53 per cent of 108 cases on the left. In most reports this factor is not mentioned. In this connection, we were at first

* Personal communication from Thomas J. Duffield, Registrar of Records, New York, N. Y.

impressed by the additional fact that in a recent analysis of over 500 cases of tongue cancer at the Memorial Hospital, there was, likewise, a greater incidence (57 per cent) on the left. Superficially considered, these several data might seem sufficiently consistent to suggest an actual left-sided preponderance of intra-oral cancer, but when the older literature is investigated, it is found that about an equal number of investigators have reported a right-sided trend in lip cancer (Janowsky,²⁷ Rowntree,⁵⁰ Woerner,⁶⁶ and Loos³³). Kennedy,³⁰ dividing the lip into three areas, found an equal incidence in the right and left thirds. Since it is well-known that in the case of alternates the laws of chance favor moderate one-sided shifts rather than exactly equal distributions, especially when the number of cases is small, the cautious observer must conclude that such irregularities as those mentioned above are purely coincidental.

Causative Factors—In lip cancer, the entire labial mucous membrane usually shows some evidence of chronic irritation. Such evidence may appear in the form of a scaly cheilitis, excessive dryness, multiple keratoses, leukoplakia, epidermization, or a tendency toward vertical folding and fissuring.

In almost 20 per cent of our series, there was a definite history of frequent "fever blisters," chapped lips, fissures, excessive sunburn, or an habitual tendency to bite or chew the lips. It is rather difficult, however, to assay the relative etiologic significance of these and of the several other chronic irritants and their resultant mucous membrane changes, which will be described below.

Climate, Exposure to Weather, and Occupation—It has been repeatedly noted in the literature that cancer of the lip (as well as of the exposed skin of the face and hands) is common in outdoor workers such as farmers, sailors, ranchers, etc., who undergo unusual exposure to the dry, irritating effects of the wind and sun. By virtue of its position, the lower lip (especially in prognathism) is more subject to such effects than is the upper lip, which may be additionally protected by a mustache. It is well-known that exposure to cold and salt spray produces keratoses of the exposed skin and lips in sailors. Cowan¹³ has recently discussed the high incidence of facial skin and lip cancer in the general population in the mountainous plateaus of Utah. The climate in these high altitudes combines to an unusual degree such factors as dryness of air, alkali dust, uninterrupted sunshine during the daylight hours, and a high component of actinic radiation through an atmosphere which is usually clear of clouds and smoke.

In the present series of patients, drawn mainly from an urban population, the percentages of outdoor and indoor workers were about equal. It is probable, however, that no special significance can be attached to these figures, since the normal occupational distribution in a large metropolitan center is impossible of accurate determination. Lane-Clayton,¹² in a series of about 1,000 cases collected from the literature reports that over 80 per cent occurred among outdoor workers, but she gives no information as to the occupational distribution in the population samples, except in the report of 176 cases by Janowsky,²⁷ who found the proportion of outdoor workers in his lip cancer

group to be about the same as in the general population from which his cases were drawn. Ahlborn¹ states that 90 per cent of his patients were outdoor workers, but he fails to give the normal occupational distribution of the general Swedish population.

It has seemed significant in a few individual cases in our series that a carpenter or cobbler has given a history of habitually holding nails in the mouth, a practice which the patient himself has quite reasonably believed to be the cause of his cancer.

Tobacco—That the smoking of tobacco in itself is directly responsible for the development of intra-oral cancer, is an old belief which, though undoubtedly founded in fact, nevertheless, is not well-supported by any statistical evidence thus far adduced. We refer here to the general effects of tobacco and not to those relatively rare instances in which cancer may arise on the lip at a point where the transmitted heat and the rough surface of a clay pipestem combine as chronic irritants in so-called "pipe-smoker's" cancer, or to those instances in which cancer arises in the leukoplakic tongue of an excessively heavy smoker. In about 11 per cent of our series, the patients gave histories of irritation from a pipestem or a tendency of cigarettes to stick to the lip at or near the site of a subsequently developing growth. Although in some of these instances a causal relationship is probable, we believe that, on the whole, no greater credence should be given to such statements by patients than to the average alleged association between a trauma and a subsequently developing cancer. At any rate, it is obviously not so much the tobacco *per se* which is responsible in these cases, but rather the excessive indulgence and the mechanical contrivance used.

When an attempt is made to prove such an effect of tobacco statistically, the calculations, in our opinion, always remain inconclusive. In our series of lip cancers, over 70 per cent of the patients admitted the use of tobacco in some form, and similar one-sided figures have been employed frequently to prove a direct causal relationship, disregarding the fact that normal healthy adults are addicted in about the same degree. To investigate this subject thoroughly, one would be faced with such difficulties as evaluating the relative effects of various degrees of indulgence, the influence of recent or remote past addiction, and the several forms of the habit.

We suspect that the emphasis often placed upon the cancerigenic influence of the tobacco habit is to some extent influenced by the ubiquitous moralistic propaganda against the "filthy weed." Once raised, the question has been discussed to a far greater extent than its importance merits in attempts at honest appraisal by the more open-minded and tolerant. Although admittedly an important factor in a few individual instances, the production of cancer is certainly one of the less harmful effects of tobacco. One often encounters similar Puritanic overemphasis with regard to the rôle of alcohol in the causation of various diseases.

Syphilis—In the present series, the incidence of syphilis, as shown by positive Wassermann tests, was about 10 per cent. This figure is almost twice the general incidence, namely, 6 per cent, in white males of a correspond-

ing age (56 years), according to Usilton⁶⁰ The disparity of 4 per cent between these two figures indicates the relatively moderate influence of syphilis in the etiology of cancer of the lip The published percentages of syphilitics among lip cancer patients vary from 2 per cent²⁹ to 20 per cent⁵³ The degenerative mucous membrane changes produced by chronic syphilis (chronic glossitis, leukoplakia, etc) are much more pronounced in the tongue and mucosa of the cheeks than in the lips, and it is obvious, therefore, that syphilis should be less prominent in the etiology of cancer of the lip than in growths in these other intra-oral sites

Defects in Dental and Oral Hygiene—The lips are also less subject to chronic irritation from sharp or worn teeth than are the tongue and the buccal mucosa, but occasionally a causal relationship is suggested by one or two very sharp teeth in the lower jaw opposite the growth In the present series, however, direct dental irritation could be demonstrated but rarely, and 13 per cent of the patients were edentulous In only about 5 per cent was it noted that the dental hygiene was good, but in interpreting this figure one must consider that the great majority were clinic patients in whom, as a class, good dental hygiene is rare

Leukoplakia—In the present series, no careful routine survey was made to discover very early or slight evidences of leukoplakia, but in about 28 per cent of the patients, well-established, easily demonstrable leukoplakia was noted on the lips, the tongue, or the cheeks The presence of some degree of leukoplakia in the oral mucous membranes after middle age cannot be considered particularly abnormal since, in the majority of cases, it represents simply a response of the mucous membrane to mild chronic irritation and, as such, is a part of the natural aging process comparable to the almost universal mild senile changes, including keratosis of the skin, which begin at, or soon after, middle age

In a recent investigation carried out at the Memorial Hospital, 100 males and 100 females, all over 40 years of age, and without any intra-oral complaint, were carefully examined for intra-oral leukoplakia Some degree of leukoplakia was found in 50 per cent of the males and in 10 per cent of the females, so slight in many instances, however, that the condition would usually be overlooked in the average examination In 12 per cent of the males, the lesions were well-established and easily recognizable even on cursory inspection Some idea of the etiologic significance of leukoplakia in lip cancer can be obtained by comparing the incidence of well-established leukoplakia in our series of lip cancers (28 per cent) with the above-mentioned 12 per cent in the otherwise normal adult male population

Acute or Chronic Trauma—In any large series of cancer cases, there are, invariably, some patients who attribute the beginning of the growth to an acute trauma In the present series the following were alleged A cut with a razor, an abrasion by a corn stalk, an injury with a lollypop stick, a blow with the fist, severe accidental biting of the lip, and a scratch by a fish bone It is our opinion that in most such instances the injuries were purely coinci-

dental, since we doubt the capacity of a single acute trauma to produce cancer in an otherwise normal mucous membrane

Contact Implantation of Cancer —It has been believed by many that cancer can be transplanted by contact from a primary lesion to overlying mucous membrane. Instances of this character have been reported as occurring from one lip to the other, from one oral mucous membrane to another, from one wall of the rectum to the opposite, *etc.* To the surgeon who has performed tissue transplants, such as skin, fascial, tendon, and other such grafts, under necessarily aseptic technic, the possibility of the accidental grafting of an infected surface cancer to an unbroken opposing mucous membrane appears exceedingly remote. It seems to us that the reported instances¹² of contact implantation from one lip to the other are undoubtedly cases of multiple cancer.

HISTOPATHOLOGY

Histologic examination will reveal some form of squamous carcinoma in practically all lip cancers. About half of our cases were squamous carcinoma Grade II, and one-third were Grade I, with Grades III and IV making up less than 2 per cent. In our opinion, the reported instances of basal cell carcinoma occurring on the lip should not properly be included in this group, since, as previously mentioned, they obviously arise in the skin apart from the vermilion border and, therefore, should be classified with other facial skin cancers. To include these basal cell growths tends only to confuse and obscure the true clinical significance of the term *cancer of the lip*. Adenocarcinoma arising in the minor salivary and mucous glands of the lip occurs occasionally, but there was none in the present series. Spindle cell carcinoma was found in three cases. This rare and highly malignant tumor usually arises in scar tissues, in most cases either in the mucous membrane of the lip or in the adjacent skin. One of us (H. M.) and Stewart³⁷ have recently reported eight cases of this tumor, four of which occurred in the region of the lips.

SYMPTOMS, MORBID ANATOMY AND CLINICAL COURSE

In its early and moderately advanced stages, lip cancer is a relatively benign disease, and the first and almost the only symptom is the presence of the primary lesion. Even in the advanced stages the growth on the lip itself disturbs no vital function, and for this reason, in most of the uncontrolled cases, death is due to dissemination of the disease either to the cervical nodes or, less often, to the viscera. If untreated, the clinical course is usually slow and of long duration, and the patients, as a rule, remain in fairly good general condition until the disease is far advanced. In this series, the average length of life of the unsuccessfully treated patients was about 43 months after the onset of symptoms.

The Primary Lesion —Frank ulceration of the growth accompanied by a definite alteration in the surface contour of the lip is seldom a prominent early finding, but it practically always occurs when the lesion has reached a size of 5-7 mm. In some instances, the first objective symptom is a firmly attached, superficial crust or scale rather than a true ulcer (Fig. 1). Bleeding occurs

A

B



FIG 1—Early cancer of the lip. Most patients with lip cancer seek medical advice when the lesions are between 1 and 1.5 cm in diameter. At this stage the lesion commonly consists of a flat slightly raised painless and nontender ulcer of about ten to 12 months' duration. The edges tend to be raised and rolled. At this stage metastasis has taken place in about 10 per cent of cases, as judged on the basis of the clinical presence of involved nodes on admission or their later development after control of the primary lesion. (A) Before treatment. (B) Healed condition after roentgenotherapy showing minimum of scarring and cosmetic deformity.

A

B



FIG 2—Moderately advanced cancer of the lip. When lower lip cancer approaches 2 cm in diameter, there is usually marked ulceration of the surface. The growth may fungate or there may be an excavated ulcer with indurated edges and infiltration to a depth of 8-10 mm. Metastasis has taken place in about 15 per cent of the cases, as determined by the clinical presence of metastatic nodes on admission or their later development after control of the primary lesion. (A) Before treatment. (B) Healed condition after treatment by combination of external and interstitial radiation.

CANCER OF THE LIP

when this crust or scale is detached There is usually palpable induration well beyond the borders of any visible lesion Pain and tenderness are characteristically absent The patient is likely to regard an early lip cancer as a



FIG 3—Advanced cancer of the lip treated by surgical excision and plastic closure The disease in this case was of six years' duration and had invaded practically the entire horizontal diameter of the lip, extending deeply into the free border and causing marked ectropion No metastases were demonstrable clinically This patient has remained well and free of disease for six years



FIG 4—Advanced cancer of the lip of four years' standing, without clinically demonstrable cervical metastases In this clinical form of the disease (A), the growth invades the lip deeply, without marked erosion or ulceration (B) Immediate postoperative condition The growth has been widely excised and the defect closed by advancing the lateral edges and in addition, by bringing down an Estlander's flap from the upper lip (C) Final healed condition The patient has remained free of disease for five years

"cold sore" or a "chapped lip," and usually fails to seek medical advice until the growth has reached a diameter of about 1 cm In the present series, of those cases in which the exact size of the lesion was stated (329 cases), only about 39 per cent of the primary lesions were 1 cm or less in diameter, 33

per cent 1.1 and 2 cm, 13 per cent between 2.1 and 3 cm, and 15 per cent over 3 cm. In 15 cases (4 per cent), practically the entire lower lip was involved when the patients applied to our clinic.

When the growth becomes more advanced, it usually presents a flat, slightly raised, coarsely granular and indurated ulcer which fixes and renders inelastic the volume it occupies (Fig. 2). Sometimes the edge of the ulcer becomes raised, rolled, and slightly undermined. After reaching this stage, the growths may be classified into two general groups: (1) The less malignant, which fungate from the surface without deep infiltration or erosion, and (2) the more malignant, which tend to invade deeply and erode the substance of the lip. Fungating tumors may reach a size of 6-7 cm with little or no local destruction of tissue. On the other hand, bulky tumors may infiltrate deeply with only a moderate degree of ulceration and erosion (Figs. 3 and 4). In still other instances, there is wide ulceration and destruction of the lip without deep invasion. Various other combinations of these clinical forms may occur. After a period of one to two years, the growth often extends into the cheeks past the commissures into the gingivobuccal gutters, onto the lower alveolus, and even into the floor of the mouth. The progress of the disease is sometimes so slow that after two or three years the growth may be only 3-4 cm in diameter without evidence of cervical metastases.

The average duration of symptoms before admission in the present series, from patients' statements, was about 15 months, which is an indication of the slow and relatively benign course of this tumor. The shortest duration was two weeks, as stated by a patient whose lesion was 2 cm in diameter on admission, a size which indicated a much longer duration. The longest alleged durations were 15 and 17 years, respectively, in both of these cases the patients gave histories which, though inadmissible without further proof, were nevertheless difficult to refute.

Cancer of the Upper Lip—This anatomic form of the disease is relatively uncommon. In our series there were 21 cases (6 per cent). As has been previously stated, the upper lip is less subject to chronic irritation than the lower, and malignant growths of the upper lip follow the general rule that spontaneous cancer is more malignant than that which arises on the basis of chronic irritation. These upper lip cancers usually ulcerate soon after they arise, grow rapidly, and metastasize early to the preauricular and/or infra-parotid lymph nodes, where the growth soon perforates the node capsule and infiltrates widely. In our 21 cases, metastases eventually occurred in ten (48 per cent), as compared to 30 per cent in the lower lip. Seven of the patients, with upper lip cancers which metastasized, eventually died (33 per cent). The prognosis of cancer of the upper lip is definitely worse (41 per cent five-year cures in the determinate group) than cancer of the lower lip, and the clinical course from the onset of symptoms in uncontrolled cases is relatively short (21 months in our fatal cases as compared to 43 months in lower lip cancer).

METASTASES

As a rule, metastasis in lip cancer occurs later in the course of the disease than in cancer of the tongue, floor of the mouth, or tonsil. In the present series, despite an average duration of the primary lesion of 15 months, the incidence of palpable metastases on admission was only 29 per cent. After admission, about 8 per cent subsequently developed metastases, so that, finally, a total of about 37 per cent presented metastases some time during the course of the disease. In this series, therefore, 63 per cent of the cases had no metastases at any time—indicative of the factor which, more than any other, is responsible for the relatively high cure-rate in lip cancer. When the primary lesion was under 1 cm. in diameter, the incidence of palpably metastatic nodes on admission was only 3 per cent. When the diameter was less than 2 cm., the incidence increased to about 8 per cent.

Except when the disease arises on the upper lip, the position of the first node involved and the later progress of cervical metastases tends to be rather orderly, that is, the nodes most often involved are the submaxillary (over 50 per cent of the cases which metastasize) or submental (about 8 per cent) of the corresponding side, with orderly progression from these areas to the upper deep cervical and later to the middle and lower deep cervical regions. These orderly tendencies depend not only upon the well-differentiated and rather uniform histology of the growths in this area, but also on the anatomy of the lymphatics of the lip. Crossed or bilateral metastases may develop, especially when the primary lesion is near to or crosses the midline of the lip. In the present series, there were bilateral submaxillary metastases in about 11 per cent of the lesions which metastasized.

TABLE I
INCIDENCE OF CERVICAL METASTASES IN LIP CANCER
According to Size of Primary Lesion

Size of Lesion	No. of Cases	Present on Admission	Developed After Admission	Total Developed During Course	None at Any Time
Under 1 cm.	33	1 (3%)	1 (3%)	2 (6%)	31 (94%)
1 to 1.9 cm.	118	10 (8%)	11 (9%)	21 (17%)	97 (83%)
2 to 2.9 cm.	49	11 (22%)	5 (10%)	16 (32%)	33 (68%)
3 cm. and over	60	29 (48%)	8 (13%)	37 (61%)	23 (39%)
Entire lip	5	2 (40%)	0	2 (40%)	3 (60%)
Not stated	48	37 (77%)	2 (4%)	39 (81%)	9 (19%)
Total	313	90 (29%)	27 (8%)	117 (37%)	196 (63%)

The incidence of cervical metastases in relation to the size of the primary lesion on the lip is given in Table I. It is interesting to note that metastases occasionally occur very early when the lesions are 1 cm. or less in diameter on admission (3 per cent). In our series, the incidence markedly increased with the size of the lesion up to 2 cm. Between 2 and 3 cm. diameters, the incidence of metastases on admission more than doubled, and again increased by about 50 per cent in lesions over 3 cm. Following control of the primary lesion, the subsequent incidence of metastases increases only slightly as the size of the lesion increases, and it would appear that if a growth has reached

a size of more than 3 cm without metastasizing, the chances of subsequent development of metastases is very slight (13 per cent)

Once metastases from the lip have developed, then further dissemination tends to be somewhat less rapid than in many other forms of intra-oral cancer. If not controlled, the growth finally perforates the capsules of the nodes, infiltrates the surrounding tissues, and becomes fixed to the mandible or other deep structures and eventually to the skin. Such nodes often suppurate, perforate the skin, and drain on the surface. Until the advanced stages, however, metastasis from lip cancer tends to remain above the level of the clavicle, although general dissemination eventually occurs more frequently than is usually realized. In a survey of the autopsy records of the Memorial Hospital, it was found that in 14 patients dead of lip cancer, visceral metastases had occurred in four (29 per cent). Dissemination below the clavicle should occur even more often from cancer of the tongue or the pharynx where the relative proportion of anaplastic growths is higher. Autopsies on 50 patients dead of tongue cancer, at the Memorial Hospital, revealed distant metastases in 20 (40 per cent).

In a survey of the literature, we have been unable to find other conclusive data on the subject of visceral metastases in lip cancer. Burke⁹ and Price¹⁵ report that in four and eight autopsies, respectively, on patients dead of lip cancer, there were no metastases below the level of the clavicle. Although these findings differ from ours, the fact remains that the total number of autopsies in all these series is not great. Our small series of lip cancer autopsies may have shown an abnormally large percentage of disseminated metastases, and it may be a coincidence only that the cases of Burke and Price showed none. On totaling these three series (26 cases), however, the incidence is still about 15 per cent. It is more difficult to explain and to accept the validity of the conclusions drawn by Crile,¹⁴ who reports that Hitchings, in a collected series of 4,500 patients dead of cancer of the head and neck (not lip cancer alone), found that less than 1 per cent showed distant metastases. One who has closely followed the terminal stages of the various forms of intra-oral cancer, and has seen autopsies in large numbers of these cases cannot help wondering what actually caused death in Hitchings' collected series, if less than 1 per cent had visceral metastases. Is it possible that many of them were postoperative deaths following neck dissection or excision of the primary lesion? Crile does not state whether the anatomic diagnoses with reference to generalized metastasis were confirmed by postmortem examinations, but in the absence of such a statement it seems probable that most of the final diagnoses were made on clinical observations alone. If a large percentage of Hitchings' series were postoperative deaths, then it is obvious that the cases must have been operable and fairly early, and that for this reason alone dissemination of the disease below the level of the clavicle would have been rare.

Anatomy of the Lymphatics of the Lip—According to Most,⁴⁰ Sassi,⁵² and Rouviere,⁴⁹ the lymphatics of the lower lip arise in the vermilion border

as a fine capillary network (Fig 5) This network combines to form several main collecting trunks which run downward over the chin into the submental and submaxillary regions In the midline, there are fairly numerous anastomoses which account for the rather frequent crossed or bilateral metastases

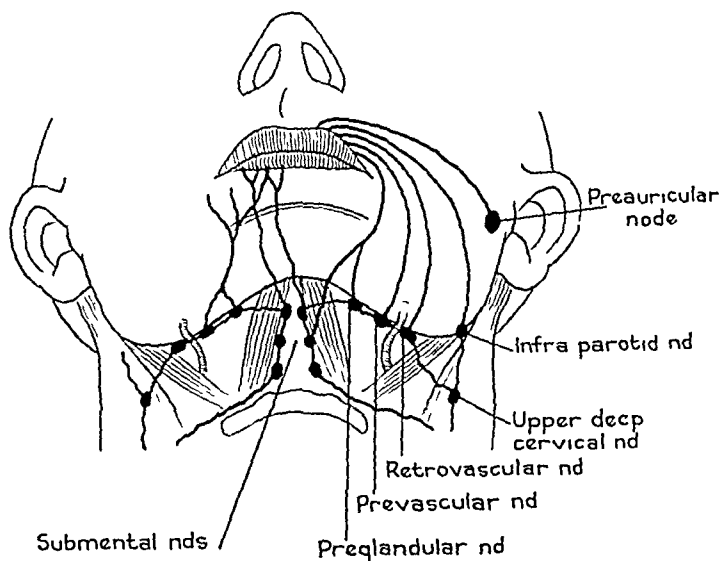


FIG 5—Anatomy of the lymphatics of the lip (After Rouviere ¹⁹) The lymphatics of the lower lip drain into the submental, submaxillary and, eventually, into the upper deep cervical lymph nodes Metastases may occur on the side opposite the lesion by anastomosis across the midline The lymphatics of the upper lip drain into the preauricular, the infra-parotid, the submaxillary, or the submental nodes

from growths which are near to or cross the midline All of the lymphatics of the lower lip drain into the submaxillary and submental lymph nodes Of the latter node groups, the most important is the submaxillary, which lies under the lower edge of the mandible at the crossing of the facial vessels and consists of the prevascular and retrovascular nodes, respectively The submental region contains a group of several nodes Both the submaxillary and submental groups drain into the upper and sometimes into the middle nodes of the jugular chain

The lymphatics of the upper lip drain into four node groups, namely, the preauricular, the infra-parotid, the submaxillary, and the submental In our experience, the first metastases from the upper lip occur most often in either the preauricular or infra-parotid nodes and then progress rapidly to the upper and middle nodes of the jugular chain

DIAGNOSIS

Although the physician as well as the patient may frequently procrastinate, one seldom finds such serious errors in the diagnosis of lip tumors as are made in lingual cancer, where growths are often treated for long periods under the mistaken diagnosis of syphilis or dental trauma Except for those lesions which are discussed below, the lip is not particularly susceptible to any disease likely to be mistaken for cancer, or *vice versa* There is no portion of the anatomy which is under closer observation by the patient and

his friends than the lips, and no abnormality in this region can long escape attention. Delay in diagnosis and treatment (averaging about 15 months in our series) is due mainly to the absence of distressing subjective symptoms. In 10 per cent of the present series, the first physician consulted had prescribed topical applications of various sorts (usually salves) for periods of several weeks or months. Such lack of diagnostic acuity can be ascribed mainly to indolence on the part of a physician who may hesitate to make any positive diagnosis which would entail a more definite recommendation for active and aggressive treatment.

Although it may seem heretical from the standpoint of cancer education to say so, our figures indicate that a moderate delay in diagnosing lip cancer does not affect the prognosis, for in the present series the cure-rate, in lesions up to 1 cm in diameter (moderately advanced), was 100 per cent. The main advantage of early diagnosis is the superior cosmetic result in smaller lesions following treatment by either radiation or surgery.

Biopsy is essential for purposes of record in lip cancer as in all other forms of this disease. In small lesions (3-4 mm in diameter), the removal of a biopsy specimen before treatment is usually not practicable, and if treated by radiation these early cases, lacking histologic confirmation of the diagnosis, should not be included for statistical purposes as cured cancer. If treated surgically, the excised tissue is always available for histologic examination. In lesions over 3-4 mm, a small wedge should be taken in all cases before treatment by radiation, when treated surgically, the question of preoperative biopsy in these lesions is the responsibility of the surgeon. In some cases, the clinical diagnosis may be so obvious as to render biopsy unnecessary, but to widely excise a tumor of the lip under a mistaken clinical diagnosis of cancer should be considered a reproach to the operator.

Papilloma—The lower lip, like all other oral mucous membranes, occasionally gives rise to papilloma. Although such benign lesions usually present the warty, fungating appearance typical of papillomas elsewhere, there may occasionally be frank ulceration and some erosion. In typical lesions, the diagnosis may be suspected from the clinical appearance but should always be confirmed by biopsy (repeated if necessary), the specimen being taken from the edge and base rather than from the apex or the surface of the growth. From the practical standpoint alone, and aside from purposes of record, accurate diagnosis in these cases is of minor importance, since the treatment for cancer and papilloma is the same.

Keratosis of the Lip—In persons who spend much time out of doors, sunburn, chapping, and fissuring of the lower lip frequently occur, and the mucous membrane undergoes definite changes resulting eventually in epidermization and leukoplakia. Keratosis often occurs and may be single or multiple and cover large areas of the lower lip. In persistent cases of this character, the diagnosis as to the presence of early cancer may be not only difficult but impossible. When such suspicious precancerous lesions are widespread, radical treatment, either surgical or radiologic, to the entire lower

lip is rarely justified. Even when cancer eventually develops in these doubtful cases, the clinical course is relatively slow, and, therefore, one may withhold aggressive treatment until there is definite clinical evidence of cancer in the form of a progressive lesion persisting at one or more points for periods of several weeks or months. While under such observation, the lip should be protected from further exposure to sun and weathering and treated by the application of such protective ointments as cocoa butter. Once decided upon, the treatment of doubtful keratoses, whether by radiation or surgery, should be just as thorough as when the diagnosis of cancer is certain.

Herpes—An apprehensive patient frequently seeks medical advice because of herpes, a lesion which may persist through its various stages for several weeks before healing. The history of its sudden appearance with pain is one of the most valuable points in differential diagnosis.

Syphilis—Primary chancre and secondary syphilids may occur on the lower lip, and their chronicity and the relative absence of pain and tenderness may raise some doubt as to the possibility of cancer. Since any syphilitic lesion of the lip is extremely rare, this question of differential diagnosis is of little practical import. Apparently, this fact is not universally appreciated by the medical profession, for in seven cases of our present series (2 per cent) antiluetic treatment had been given over periods of several weeks to months before the correct diagnosis of cancer of the lip was suspected. Simmons⁵⁵ has reported cancer developing in the scar of a chancre which had been present two years previously.

Other benign lesions such as tuberculosis, simple ulcers, retention cysts, muscle xanthoma, and hemangioma are either rare or present no problem in differential diagnosis.

Diagnosis of Cervical Metastatic Cancer—An essential finding for the clinical diagnosis of cervical metastatic cancer is the palpable presence of enlarged lymph nodes, without which it must be assumed for all practical purposes that metastases are absent. The fact that cervical lymph nodes are palpable, however, does not necessarily mean that they have been invaded by cancer, nor does it signify even that they are enlarged. A careful search will reveal palpable cervical lymph nodes in about 50 per cent of all normal persons (at the lower edge of the mandible at the crossing of the facial vessels, in the submental regions, or in the carotid bulb area), and, therefore, case histories which state that "nodes are not palpable" are confusing since the reader is left uncertain as to whether the examiner mistakenly considered that all palpable nodes were metastatic or otherwise diseased.

(In many published reports on intra-oral cancer, cervical "glands" are spoken of as being "present," "absent," "palpable," "enlarged," "soft," "hard," *etc*, and when no confirmatory histologic data are given the helplessly confused reader is left to interpret the clinical significance of such vague observations and terminology. The fault here is twofold. In the first place, the examiner has evaded the responsibility of stating whether or not he believes metastases to be present. If the examiner expresses no definite opinion, how can the reader be expected to form one on such equivocal evidence? In the second place,

the term "gland" or "cervical gland" is inexplicit and confusing. While we concede that the term "lymph gland" has the sanction of anatomists, it should be remembered nevertheless that the neck contains many glands beside those in the lymphatic system, namely, the parotid salivary, the submaxillary salivary, the thyroid, and the parathyroid. It is unfortunate, therefore, that the term "gland" should ever have been applied to cervical lymph nodes, since such a designation is too inclusive and apparently has led many physicians to believe that metastasis commonly takes place in any or all of these various glands. This error is often a cause of anxiety to the inexperienced who discover the presence of palpable but otherwise normal thyroid and submaxillary or parotid salivary glands. If the term "node" or "lymph node" were used instead of "gland" or "lymph gland," much of this confusion would be eliminated.)

Many writers infer that palpable lymph nodes must be either "metastatic" or "inflammatory," a conclusion which does not necessarily follow. In cases where there is marked intra-oral and dental sepsis or an infected cancer, sepsis, alone, may obviously be responsible for some enlargement of the cervical lymph nodes. In the absence of other symptoms or of abnormal enlargement, moderate bilateral and symmetric palpability of lymph nodes is presumptive evidence of their benign character. The unilateral or asymmetric enlargement of one or more nodes is always indicative of a serious pathologic process, and when accompanied by induration without tenderness this finding is one of the most valuable criteria in the diagnosis of metastatic cancer.

Accuracy in the clinical diagnosis of metastatic lymph nodes is achieved only by experience, and by repeatedly checking definite preoperative opinions against postoperative histologic examinations or aspiration biopsies. In clinics, where routine neck dissections are performed for both prophylactic and curative purposes, the accuracy of clinical diagnosis appears to be low (from the published reports,^{20 30 58} 20-33 per cent) even in cases where the nodes are said to be "palpable." Taylor and Nathanson,⁵⁸ in reporting a collected series of lip cancer, state that out of 186 neck dissections, "palpable" nodes were histologically positive in only 17 per cent. Kennedy,³⁰ in a similar collected series of 64 patients, in whom "no nodes were felt," found that 14 per cent were positive when histologically examined. These authors were not themselves personally responsible for the accuracy of the diagnoses in these cases which were collected from general hospital admissions, the clinical descriptions were made by a number of observers—in many instances, probably by junior members of the house staff. These findings, therefore, should not be taken to represent more than the judgment of the average examining physician who may have little special interest in cancer. The decisions to operate and the operations themselves in the above-mentioned series were also divided among a number of surgeons. For these reasons, what appears to be such inaccuracy in diagnosis is probably not representative of the best effort of the surgeon who performs neck dissections. In any event, rather indifferent diagnostic skill must be expected when the treatment is the same (neck dissection) whether nodes are said to be "palpable," "not palpable," or otherwise. Especially where prophylactic

neck dissections are routine, the *tactus eruditus* necessary for reasonable accuracy in diagnosis is superfluous, and, therefore, is not likely to be developed. With regard to metastatic lymph nodes, if the term "palpable" were used only in its strict adjectival sense and lost all sanction as an expression of the clinical diagnosis, this fault would soon be remedied.

TREATMENT OF CANCER OF THE LIP

As is also true in most other intra-oral tumors, the treatment of cancer of the lip consists of two separate problems: (1) The care of the primary lesion, and (2) the cervical metastases.

The general plan of management should be based on a consideration of the special anatomic and clinical features of this form of the disease. Cancer of the lip can in most cases (at least 65 to 70 per cent) be diagnosed early and treated before metastasis has taken place. In evaluating treatment methods for the primary lesion, it is of significance that the lower lip is readily accessible to both surgery and radiation. Radiation methods may be employed in adequately heavy dosage with the neighboring normal tissues adequately shielded from undesirable reactions. Large portions or even the whole of the lower lip may be excised and replaced by plastic repair without great difficulty. For these reasons, either radiation or surgery can be employed with equally good chances of cure in the uncomplicated primary lesion. The selection of the treatment method in an individual case must, therefore, be made upon some basis other than the supposed superiority of one or the other method from the standpoint of cure alone—the most important considerations being the cosmetic result and the expediency of one particular method as regards its availability, the training and experience of the surgeon, the period of morbidity, and the general condition of the patient.

A survey of the literature will reveal that a number of methods with varying technics, both surgical and radiologic, have been used successfully for the treatment of the primary lesion in this disease. These methods include surgical excision, cautery excision, electrodesiccation, roentgenotherapy, surface and contact radium application, interstitial radon seeds and needles of radium and radon (² ²⁰ ²⁶, ²⁹, ³⁸ ⁴² ⁴³). Those who have had broad experience with these several methods will agree that none has any exclusive superiority over the others in all stages and clinical forms of the disease, either from the standpoint of cure or the functional and cosmetic result. The comparative merits of radiation and surgery in the treatment of cancer in general cannot be very convincingly proved by the end-results of either in cancer of the lip. It is significant that proponents of the exclusive use of one or the other of these methods commonly present the results obtained in the treatment of early lip cancer as proof of the merits of one particular method to the exclusion of the other for all malignant tumors. Cancer of the lip is the least malignant anatomic variety of intra-oral cancer, and except in the later stages the prognosis is reasonably good with any accepted method properly employed. In the advanced cases where unusual

difficulty is encountered, the fan-minded surgeon will gratefully and willingly employ all worth while methods in combination

The time-honored method for the treatment of lip cancer is surgical removal in the form of a V-shaped wedge for smaller growths and of extensive plastic procedures for those more advanced. While capable of curing the local lesion in practically all early cases, if properly applied, these surgical procedures always produce cosmetic defects, the gravity of which depends on the extent of the excision. Since the lower lip is such an important structure from the cosmetic standpoint, radiation measures have long been preferred by many, especially in the earlier lesions. When judiciously employed, such treatment will produce a high percentage of cures with a minimum of deformity.

On the other hand, when a lesion is further advanced and when it has replaced or eroded a volume of 1.5 cm. or more of the lower lip, the treatment, even by radiation, may leave a tissue defect or a marked sclerosis. From the functional and cosmetic standpoints, these radiation sequelae in the advanced cases may be more undesirable than the deformity following surgical removal. Such remaining radiation defects often require plastic repair after healing, and in these, since a perfect cosmetic result is unattainable by any means, surgical excision in the beginning is often the more practical and expeditious method. Certain other widely infiltrating lesions are often best dealt with by combinations of radiation and surgery.

As has already been mentioned, the management of the cervical metastases presents a problem separate from that of the primary lesion. Considerable controversy exists as to whether prophylactic treatment, either radiation or surgery, should be used in the absence of clinically positive metastases. There is also a difference of opinion as to whether surgery or radiation is the more efficacious in the treatment of actual metastases. We believe that an unbiased consideration of these controversial questions will demonstrate that, as in most controversies, the truth lies between the extreme viewpoints. In the discussion which follows, we shall attempt to present a fair appraisal of the relative merits and specific advantages of radiation and surgery in the several clinical forms and stages of lip cancer.

The methods about to be described are those developed at the Memorial Hospital during the last 25 years, beginning with the radiation attempts in 1914 by the late H. H. Janeway,²⁶ a surgeon who was one of the first to substitute radiation for surgical excision in the treatment of early lip cancer. As will be seen later, the methods now in use consist of either radiation or surgery or a combination of the two, depending upon the clinical course of the given case.

TO BE CONTINUED

OBSERVATIONS ON THE PREVENTION AND TREATMENT OF POSTOPERATIVE ATELECTASIS AND BRONCHOPNEUMONIA*

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THE POSTOPERATIVE pulmonary complications that are usually encountered are of two general types—those due to the retention of bronchial secretions and those due to emboli. Although emboli^{8, 9, 10, 12} are responsible for a certain percentage of complications, we believe the great majority of instances of postoperative pneumonia and atelectasis are the result of retained bronchial secretions. The emphasis in this paper will, therefore, be upon the complications resulting from the retention of bronchial secretions. Particular consideration will be given to the early recognition of the presence of bronchial secretions, to the measures for preventing the retention of secretions and to the methods for promoting bronchial drainage when retained secretions are present. When bronchial secretions occur as a result of septic or aseptic emboli, they must be managed in the same way as secretions due to other causes.

The development of postoperative complications when due to retained bronchial secretions is dependent upon two causes. One is the presence of bronchial secretions, which may be due to a mild preexisting inflammation of the respiratory tract, to the entrance of pharyngeal secretions into the bronchial tree either during or following operation, or to the formation of bronchial secretions postoperatively. The second cause is the decreased respiratory and cough efficiency associated with the operation.

The incidence of postoperative atelectasis and bronchopneumonia is importantly influenced by several factors. The location of the operative site has an important influence in determining the frequency with which these complications are encountered. They are noted most often following upper abdominal operations,²⁰ and their incidence following gastric operations is about twice as great as following operations on the biliary system. Also, they occur more frequently in patients who have chronic cough²⁵ and expectoration before operation, as symptoms of chronic bronchitis, bronchiectasis, paranasal sinusitis and asthma, as well as in patients with acute respiratory infections. Another factor is the sex difference—postoperative atelectasis and bronchopneumonia being two or two and one-half times as frequent in males as in females. This difference has been attributed to the fact that, normally, females are predominately costal breathers, whereas males are predominately

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diaphragmatic and abdominal breathers. As a result, the postoperative diaphragmatic splinting exerts a more profound reduction in the respiratory efficiency of males than it does in females. Beecher² has shown that the reduction in vital capacity following upper abdominal operations is greater in men (58 per cent) than in women (49 per cent), and that the greatest and most rapid rate of recovery takes place between the second and fourth day in women, while in males it is delayed and takes place between the fourth and sixth days. These observations suggest that the greater incidence in males is due to the greater reduction in pulmonary ventilation and to the greater reduction in the efficiency of respiration and coughing after operation. Another possible explanation for the greater incidence in males is the more frequent incidence of cough and expectoration preoperatively.

PREVENTION

As the preoperative condition of the respiratory tract may influence the development of postoperative pulmonary complications, the possibility of a small amount of daily sputum should be sought for by careful questioning,¹⁷ since this is often present and not appreciated or acknowledged by the patient unless he is particularly questioned about it. If sputum is present, care should be taken immediately before the anesthesia is begun to be certain that all secretions have been raised. Furthermore, if a history of expectoration has been elicited, the necessity for maintaining constant removal of these secretions after operation is obvious. When an acute respiratory infection is present, operations of election should be delayed for a considerable period following recovery from the respiratory infection. A delay of only a few days is usually not sufficient to allow complete recovery, and the operation preferably should be deferred until at least two or more weeks have elapsed after the acute symptoms have disappeared. Faulty oral hygiene should be corrected prior to operations of election, even when local or spinal anesthesia is used, for the reason that oral and pharyngeal secretions may gravitate into the tracheobronchial tree during sleep, unless the posture of the patient is regulated to prevent this occurrence.

The type of preoperative sedation should be chosen with care, and those sedatives which cause prolonged sleep or drowsiness after operation should be avoided. A large dose of a long-acting barbiturate, such as nembutal, is inadvisable, and if a barbiturate need be used it should preferably be of a brief-acting type. The advisability of administering atropine preoperatively has been questioned by many persons because it increases the viscosity of bronchial secretions, and we believe it should be avoided unless indicated for a definite reason, such as the prevention of excessive salivation during operations in the region of the mouth or pharynx.

Operative Considerations—The position of the patient on the operating table is of importance in preventing the gravity drainage of oral and pharyngeal secretions into the tracheobronchial tree. Especially in patients with pharyngeal secretions, the head should not be raised on a pillow as this position allows a better opportunity for the secretions to enter the trachea. In

order to overcome the normal posterior deviation of the trachea, the operating table should be inclined to a 10 or 15 degree Trendelenburg position. The normal curve of the upper dorsal spine varies, being as a rule more marked in elderly patients. The trachea accordingly has a greater posterior deviation in elderly than young persons and, therefore, as a rule the greater degree of Trendelenburg position should be used in elderly persons. However, the type of operation or the condition for which it is done may demand that the table be flat or the head of the table elevated.

The available evidence suggests that the incidence of atelectasis and bronchopneumonia is not importantly influenced by the anesthetic agent. It is desirable, however, that the anesthesia should be gauged so that the patient will awaken promptly following the operation. Schmidt and Waters²⁷ observed that the greatest incidence of pulmonary complications followed the use of ether, and the next greatest incidence followed spinal anesthesia. Brown,⁴ however, is of the opinion that the incidence of pulmonary atelectasis is greater following spinal anesthesia than with any form of inhalation or regional anesthesia. He attributes this to the fact that spinal anesthesia definitely inhibits the depth and force of respiratory movements not only during the operation but for a considerable period thereafter. Brown also believes that it is these respiratory movements (both intrinsic and extrinsic) which tend to rid the tracheobronchial tree of foreign matter or secretion.

Jones and McClure,¹⁹ in 1931, called attention to the influence of the transverse upper abdominal incision in reducing the incidence of postoperative complications. As the transverse incision is in the plane of the muscular and aponeurotic fibers of the external and internal oblique and transversus abdominis muscles, the pull of these respiratory muscles during costal excursion tends to approximate and relax the wound rather than to exert tension upon it, as with the vertical incision. Furthermore, the transverse incision offers less opportunity for injury to the intercostal nerves supplying the musculature of the upper abdominal wall. Jones and McClure observed a reduction of pain and more nearly normal respiratory excursion and pulmonary ventilation after the use of the transverse incision. They were impressed by the comfort and ease of breathing in the average short, obese patient following a gallbladder operation with the transverse incision. In a series of 125 consecutive transverse abdominal incisions, most of which were for operations upon the gallbladder, bile ducts and stomach, they noted no instance of postoperative pneumonia or atelectasis. Five patients developed pulmonary embolism which proved fatal in two instances. Jones and McClure state that two or three additional patients developed pulmonary symptoms, such as cough of mild or moderate degree, but other evidences definitely establishing a pulmonary complication were lacking. Their statistics are in striking contrast to the usual incidence of pulmonary atelectasis and bronchopneumonia, which is 5 to 12 per cent and occasionally more, in most series of gallbladder operations. During the last few years the transverse incision has been used at the University of Michigan Hospital with increasing frequency in gallbladder and other abdominal operations and at present it is used almost

routinely in gallbladder operations. Our observations in these cases agree with those of Jones and McClure in regard to the smoother convalescence. In a series of operations for chronic cholecystitis and cholelithiasis, we have found the incidence of postoperative atelectasis and pneumonia considerably lower than with the vertical incision, but not as low as reported by Jones and McClure.

Postoperative Considerations—It is highly desirable that the anesthesia and the preoperative medication should allow patients to awaken promptly following operation, thereby enabling them to cough and expectorate by the time they are to be placed in bed. In the event that the respirations are "wet" and that consciousness is not resumed shortly after operation, or that



FIG. 1.—Lateral position. Frontal bronchogram demonstrating dependent drainage of bronchial tree of uppermost lung with patient on contralateral side.

coughing is ineffectual, aspiration of the tracheobronchial tree by catheter suction or by bronchoscopy is indicated. It is believed that hyperventilation with carbon dioxide and oxygen at the conclusion of the operation is in itself not sufficient if secretions are present and cannot be raised by expectoration. When hyperventilation is used, it is generally agreed by anesthetists that a nonabsorbable buffer agent, such as nitrogen, helium or air, should be used in the inhaled gas mixture so that alveolar collapse will not result from the sole use of two rapidly absorbable gases such as carbon dioxide and oxygen.

Elevation of the foot of the bed¹³ is advisable until consciousness is resumed, unless circumstances contraindicating this position are present. A considerable degree of the Trendelenburg position is necessary to secure actual gravitation of tenacious secretions toward the pharynx.¹ The foot of the bed may need to be elevated ten to 18 inches (seven to 11 degrees) or more to cause the trachea to become horizontal when the patient is in the supine position. Even so, the posterior segment of the upper lobe and the superior dorsal and subapical segments of the lower lobe remain dependent. For this reason, it is advisable that the patient be turned on alternate sides²⁰ in order that the maximum benefit of posture will be obtained for each lung during the time that it is uppermost (Fig. 1). As the lower portion of the trachea

usually deviates slightly to the right, dependent drainage of the trachea is obtained when the patient is lying flat on the left side, but the foot of the bed must be elevated to provide dependent tracheal drainage when patient is on



FIG 2—M M, No 372675 (A) Roentgenogram Nov 19, 1938, on first postoperative day following total gastrectomy shows partial atelectasis of right lung. Tracheobronchial suction on three occasions during a period of five hours. Improvement of voluntary cough, so patient treated by alternate lateral positions, one hour on left side and one half hour on right, and by encouragement of frequent cough. (B) Roentgenogram Nov 21, 1938 two days later. Right lung almost clear. Pneumonitis has developed on left. Cough productive and effectual. Subsequent treatment by change of position at hourly and half hourly intervals with patient kept one hour on right side and one half hour on left. (C) Roentgenogram, Nov 23 1938 two days later. Return of atelectasis of right lower lobe. Left lung now clear. Position now changed more frequently than before to prevent stasis of secretions in more dependent lung. (D) Roentgenogram, Nov 28, 1938, five days later. Clinical improvement with only slight residual pneumonitis at right base.

This case illustrates the beneficial effect of the lateral position in improving the drainage of the lung which is uppermost for the greater length of time and the possibility of drainage of secretions into the dependent lung. More frequent change of position (at least every 20 minutes) would have decreased the tendency for involvement of the more dependent lung.

the right side. After consciousness has returned, the use of the lateral position should be continued by having the patient lie on alternate sides for periods of not longer than 30 minutes each, or by alternating the lateral

positions with the supine position. The obvious disadvantage of the lateral position is that it does not provide drainage of the dependent bronchial tree and it also allows secretions from the uppermost lung to gravitate into the dependent lung,¹¹ unless an uncomfortable degree of elevation of the foot of the bed is maintained. For this reason, patients should not be allowed to remain on one side for a prolonged period. Ordinarily, the maximum time the patient should lie upon one side should not be more than 20 to 30 minutes, but should be governed by the amount of secretions, being shorter when abundant secretions are present (Fig 2)



FIG 3—Hypoventilation of right lung 36 hours following sigmoid colostomy. Moderate abdominal distention. Breath sounds absent at right base until ventilation of base was obtained by coughing.

The recognition of varying degrees of pulmonary hypoventilation can be obtained by physical, as well as roentgenologic examination of the chest. The physical examination of the bases of the lungs is facilitated when the lung being examined is in an elevated position (with the patient lying on the opposite side), as this position offers the patient an opportunity to demonstrate the maximum voluntary amount of ventilation of the lower lobe of the uppermost side. Any decrease in the amount of ventilation is, therefore, of greater significance than when the physical examination of the bases is carried out with the patient lying on his back. Ordinarily, following upper abdominal operations, considerable hypoventilation of both bases exists, being greater on the right than on the left²⁴ (Fig 3). The degree of hypoventilation is influenced by a number of factors among them being the location and type of operation,²⁰⁻²² the severity of the operation, the general condition and sex

of the patient, the amount of pain and muscle splinting,⁶ the amount of abdominal distention⁷ and the degree of obesity. It is a usual finding that the decreased breath sounds at the bases of the lungs following upper abdominal operations can be materially augmented during the examination by having the patient take several deep breaths, by the deep inspiration that follows voluntary cough (Fig 4) or by hyperventilation with carbon dioxide-oxygen inhalations. We have occasionally seen patients in whom the pulmonary hypoventilation was so marked that breath sounds over the lower dorsal segments of the lower lobe could not be heard on deep breathing or after cough, but could be elicited only by auscultation during hyperventilation with 15 per cent carbon dioxide and oxygen. It is particularly recommended that the character and intensity of breath sounds be elicited during one or all of the above-mentioned maneuvers. If the intensity of the breath sounds reaches or approximates normal and if râles and rhonchi are absent, one can be reasonably certain that the bronchi are not obstructed by the secretions and that the decreased breath sounds heard at the beginning of the examination were due to hypoventilation and not to atelectasis.

Roentgenologic examination of the chest following operations on the abdomen and particularly on the upper abdomen showing varying degrees of hypoventilation, as is evidenced by elevation of the leaves of the diaphragm, decrease of costal expansion, and decreased aeration of the lungs, especially at the bases. Pulmonary hypoventilation is evidenced by a generalized haziness and loss of aeration of the lung, especially of that portion immediately above the diaphragm. Hypoventilation will appear more marked than it actually is if the roentgenograms should be made in the expiratory phase of respiration, an occurrence which is noted when patients are unable to cooperate by holding a deep inspiration while the exposure is being made. Therefore, the position of the leaves of the diaphragm and the amount of expansion of the thoracic wall should be ascertained when interpreting the nature of basal densities. Also, the roentgenologic technic used for exposure of the films must be taken into



FIG 4.—Examination of base of lungs is preferably undertaken with patient lying on the side, in alternate lateral positions, thereby improving ventilation of uppermost lung. Breath sounds that may be decreased or absent due to hypoventilation can be augmented when auscultation is done during cough (illustrated) or during hyperventilation with carbon dioxide-oxygen inhalations thus aiding in differentiation between atelectasis and hypoventilation. Rhonchi due to bronchial secretions may be detected by these maneuvers when otherwise not audible. In the illustration the incision for a gastric operation is being supported by the examiner's hand. The tube in the patient's nose is for continuous duodenal suction.

consideration in interpreting the degree of hypoventilation. As the roentgenograms will ordinarily have been made with a portable unit, and with the patient in a semireclining position, the leaves of the diaphragm will appear higher and the degree of ventilation will appear less than if they had been made with the patient in an upright position and with a standard chest unit. If considerable hypoventilation is present, the increased density of the bases of the lungs may simulate patchy atelectasis or bronchopneumonia.²⁴

Hypoventilation decreases the effectiveness of bronchial drainage by an actual reduction in the size and motility of the bronchi and by a reduction in the amount of air that can be expelled from the lungs by coughing. The reduced diameter of the bronchi interferes with the drainage of viscid bronchial secretions and lessens the to-and-fro movement of air which in itself aids drainage. The hypoventilation of the lungs lessens the available amount of air that can be expelled by coughing, thereby reducing the effectiveness of expectoration by decreasing the volume and force of the coughing act. Measures that aid in increasing the ventilation of the lungs are of preventive and therapeutic value and should include frequent change of position, deep breathing exercises, and carbon dioxide-oxygen inhalations. Carbon dioxide-oxygen inhalations are particularly helpful in increasing the ventilation of the lungs in those patients who are unable to obtain hyperventilation by voluntary deep breathing exercises.

The prompt recognition of the presence of bronchial secretions is of fundamental importance in the prevention of postoperative pneumonia or atelectasis, for the reason that retained bronchial secretions are, in our opinion, a precursor to the development of atelectasis and bronchopneumonia in most instances. The patient should be encouraged to cough at periodic intervals of at least every two hours, not only to increase the ventilation of the lungs, but, of equal importance, to determine whether the cough is wet or dry. A wet type of cough signifies the presence of bronchial secretions, and demands that the secretions be evacuated, either by coughing, which will usually be effective, or by actual suction. The character of the respiratory sounds should be elicited by auscultation with the stethoscope placed close to the patient's mouth, in order to determine whether the breath sounds are dry or whether rhonchi or wheezes are present. The presence or absence of rhonchi should also be determined by palpation and auscultation of the chest. As mentioned above, auscultation of the bases of the lungs is preferably done with the patient lying on alternate sides, both bases being examined while the patient is on each side, but particular attention being directed to the physical signs over the base of the uppermost lung. Due to the increased costal excursion of the uppermost lung and the resultant better ventilation of the lower lobe on this side, the breath sounds are heard to better advantage and rhonchi and wheezes are more often audible when the patient is in this position than when he is in the supine position. The character of the breath sounds prior to, during and following a diagnostic cough should be elicited, as rhonchi that are not present on deep breathing are often heard during the inspiration and expiration coincident with cough. When patients are unable to ventilate the

bases well on deep breathing and when the cough is weak, the presence or absence of rhonchi at the pulmonary bases should be determined by auscultation during hyperventilation with carbon dioxide-oxygen inhalations. The early detection of rhonchi is of importance because their presence is the earliest sign of partial bronchial obstruction due to secretions, occurring before the development of frank signs and symptoms of atelectasis or bronchopneumonia.

Voluntary cough is the most important single measure in the prevention and treatment of postoperative atelectasis and bronchopneumonia. The importance of an effective diagnostic or therapeutic cough should be stressed to the patient, in order to obtain his cooperation, even though the act of coughing may be attended with considerable discomfort. The patient should be instructed to take several deep breaths before each cough in order to increase its effectiveness. When the patient is in the supine position a painful abdominal incision should be supported by the nurse or surgeon by gentle constant pressure at each side of the incision, supplemented by firm compression of the costal margins. The patient should also be shown how he can aid himself by supporting the incision.

The position of the patient in bed is important in influencing the effectiveness and ease of cough. When he is in the supine position, the cough is usually more effective if the head of the bed is raised slightly than if the bed is flat or in the Trendelenburg position. Coughing is, however, usually easier and even more effective when the patient is in the lateral position. Manual support of the incision with the patient in this position is aided by the nurse or surgeon standing behind the patient, supporting the incision with one hand²³ and exerting counterpressure over the spine with the other hand. In the lateral position the patient can conveniently support the incision with one hand, which in turn can be supported by the nurse's or surgeon's hand. When tenacious secretions are being raised with difficulty, it is often necessary to offer continuous verbal encouragement to the patient, as well as manual support to the incision, so that the complete expulsion of secretions will be obtained. It is not sufficient merely to ask the patient to cough, he should be instructed how to do so and helped to do so.

The use of a small dose of an opiate (insufficient to obtund the cough reflex) is of advantage in decreasing the amount of pain coincident with coughing, thereby increasing the effectiveness of cough. Steam inhalations with menthol aid in reducing the viscosity of bronchial secretions and are of definite advantage when tenacious secretions are present. The continuous use of a steam tent provides another means for accomplishing the same purpose. Expectorants are of value and are used when they can be administered orally. When purulent bronchial secretions are present, the use of one of the sulfonamide drugs is indicated, our preference at present is for sulfathiazole in view of the fact that pneumococci are usually present.^{7, 28}

THE ASPIRATION OF BRONCHIAL SECRETIONS BY SUCTION

The prompt removal of bronchial secretions by suction is indicated as soon as it is evident that the cough is ineffectual and bronchial secretions are

being retained. Two methods are available for the removal of bronchial secretions, one by bronchoscopy¹⁷ and the other by means of a catheter introduced into the tracheobronchial tree.¹⁴ Bronchoscopy possesses the advantage of allowing visual inspection of the bronchi, and by its use one can be certain that the tracheobronchial tree is dry at the conclusion of the aspiration. In cases of postoperative atelectasis and bronchopneumonia, bronchoscopy reveals varying amounts of thick, viscid secretion which at first is mucoid and later mucopurulent. Often a tremendously large amount of secretion is present. The secretion is usually in a semifluid state and only partially occludes the large bronchi, an actual mucous plug completely occluding a bronchial orifice is an infrequent occurrence. Slight swelling and inflammation of the tracheal and bronchial mucosa are usually seen on bronchoscopic examination, and occasionally there are areas of moderate or a considerable degree of edema of the mucosa of the lobar orifices. Bronchoscopy allows the inflamed mucosa to be shrunk with a solution of pontocaine and adrenalin, and the lumen of the bronchi is thereby enlarged. Bronchoscopy also occasionally reveals a localized adherent fibrinous exudate which can be removed by aspiration or by other mechanical means (Fig 5). Our bronchoscopic findings are the same as those of others in similar cases.^{4 5 16 18 21}

Tracheobronchial suction by means of a catheter introduced through the nose and into the bronchial tree provides a readily available measure for the aspiration of retained bronchial secretion.¹⁴ This method, which has previously been designated as intratracheal suction is more accurately described as tracheobronchial suction, in that the large bronchi, as well as the trachea, are aspirated. Tracheobronchial suction can be used as an alternative to bronchoscopy in most instances when removal of secretions is indicated. It is particularly applicable when repeated aspirations are required, perhaps at hourly or two-hourly intervals. Tracheobronchial suction provides a measure which is usually quickly available when emergency aspiration of secretions is indicated, as it does not require the short delay necessary for the assembling of bronchoscopic equipment. When the amount of retained bronchial secretion is small, tracheobronchial suction will usually be sufficient. When the amount of secretion is large, we prefer bronchoscopic aspiration as the initial procedure, followed by catheter suction at frequent intervals until voluntary cough becomes effective. Occasionally, difficulty will be experienced in introducing the catheter into the trachea, and in such instances bronchoscopy should be resorted to without delay. If a patient is critically ill and cyanotic, bronchoscopy, if expeditiously performed is frequently a less upsetting measure, and oxygen can be conveniently administered through the aspirating channel of the bronchoscope while the tracheobronchial tree is being cleared by means of the aspirator introduced through the bronchoscope. Oxygen, however, can also be given through a nasopharyngeal catheter during catheter suction of the bronchial tree.

The requirements for tracheobronchial suction are a No. 16 F soft rubber urethral catheter, a suction apparatus delivering 15 to 25 lbs suction, and

connecting tubing. We prefer a catheter of the Robinson type with two openings, and it should preferably be new and not softened by repeated sterilizations. A Luken's glass bronchoscopic collecting tube is customarily

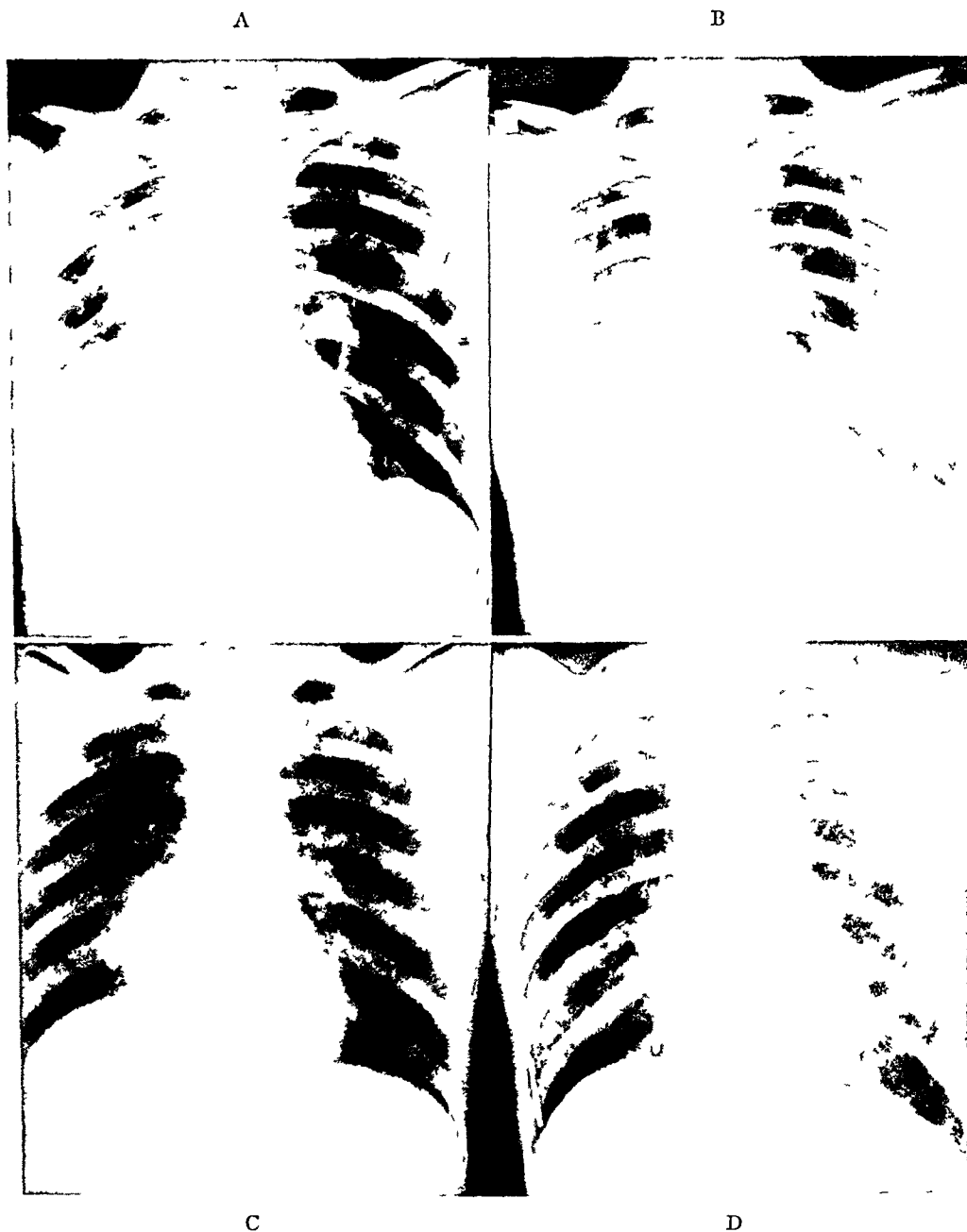


FIG 5—L. H. No. 425951. (A) Roentgenogram reveals pneumonitis and partial atelectasis right lung 28 hours following cholecystectomy and choledochostomy. Large amount of purulent secretion aspirated by tracheobronchial suction on two occasions. (B) Roentgenogram on following day. Clinical improvement but persistence of fever and large amount of purulent expectoration. In view of atelectasis of right middle lobe bronchoscopy was believed preferable to tracheobronchial suction so that middle lobe orifice could be inspected during the aspiration. Bronchoscopy revealed partial obstruction of orifice of middle lobe bronchus by fibrinous exudate, which was removed. (C) Roentgenogram three days later demonstrates residual infiltration of right middle lobe. Convalescence satisfactory. (D) Roentgenogram nine days later shows clearing of infiltration.

interposed in the system, in order to estimate the amount and consistency of the secretions and to obtain a specimen for bacteriologic examination. The open end of the collecting tube is fitted with a rubber stopper with a one-

quarter-inch hole. The hole in the stopper is intermittently occluded with the thumb so that suction will be obtained only when the hole is occluded. If the collecting tube is not available, intermittent suction can be obtained by pinching and alternately releasing the connecting tubing, or by the use of a glass Y-tube, the open end of which is intermittently occluded with the finger.

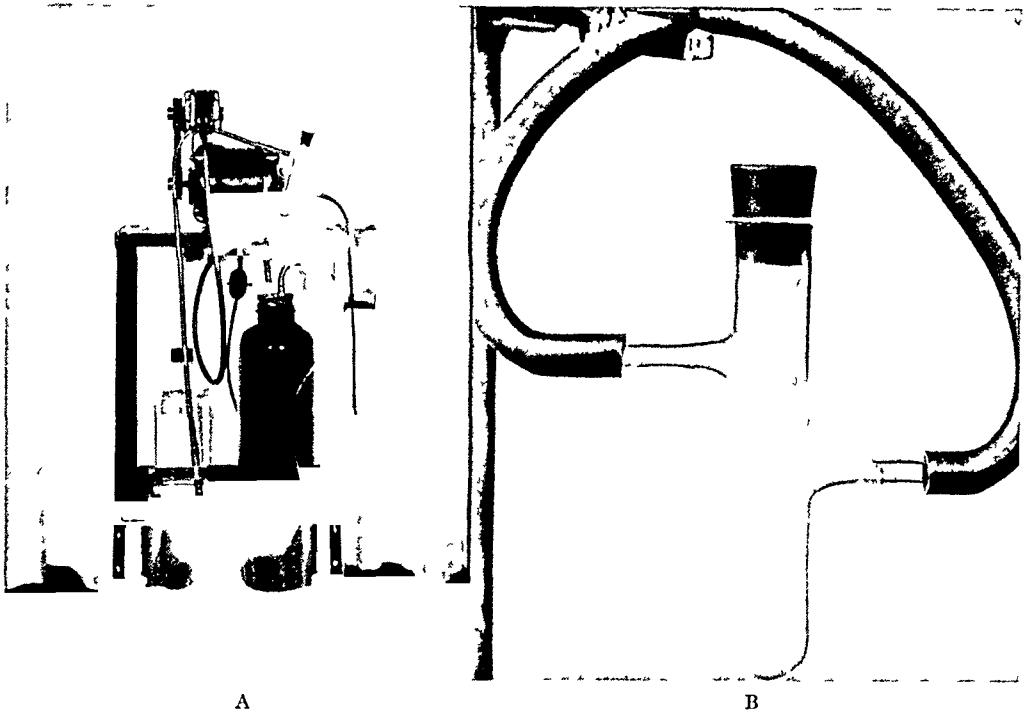


FIG 6—(A) Apparatus for tracheobronchial suction consists of suction machine, bronchoscopic collecting tube (optional) and No 16 F urethral catheter. (B) Bronchial secretions more purulent than usual removed by tracheobronchial suction.

As the amount of secretion obtained is frequently more than the bronchoscopic collecting tube can hold, a pus-trap should be interposed into the system to prevent the secretions from entering the suction apparatus (Fig 6).

The catheter is introduced into the tracheobronchial tree without the use of local anesthesia. The patient is placed in the semi-Fowler position, the neck is flexed slightly and the tongue is pulled forward by the operator in order to elevate the epiglottis. The catheter is then introduced through the nose, using the side which is the more widely patent, and it is directed posteriorly until the operator feels it touching the larynx. The catheter is then withdrawn 1 or 2 cm (Fig 7) and the patient is asked to take a quick deep breath. The catheter is then quickly advanced into the trachea during deep inspiration. If this maneuver is unsuccessful, the patient is asked to cough and the catheter is quickly advanced during the deep inspiration following cough. Unless pharyngeal secretions are present, suction is not applied until the catheter has been introduced into the trachea. During the introduction of the catheter into the trachea, the operator maintains traction upon the tongue in order to prevent the patient from swallowing. The operator is assured that the catheter is in the trachea and not in the esophagus by the

onset of coughing, the passage of air through the catheter, or by huskiness of the voice when the patient is asked to speak

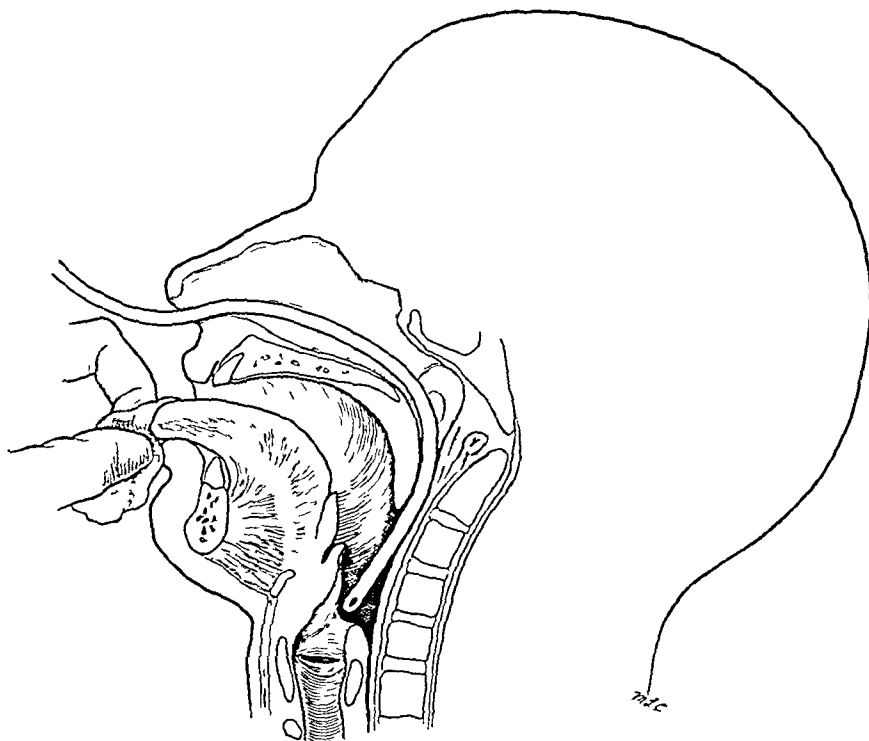


FIG 7—Diagram illustrating method for introduction of catheter into trachea. Tongue pulled forward to raise epiglottis, thereby opening passageway for catheter

After the catheter is in the trachea, the head of the bed is lowered to the horizontal position. Suction is then applied for several seconds and tracheal secretions, if present, are aspirated. The suction is then stopped and the patient is asked to take several deep breaths, following which the suction is again applied for several seconds. This sequence is repeated until the trachea is dry. The catheter is then introduced into the bronchial tree of the more involved lung. Ordinarily, the catheter enters the right bronchus, as it is more nearly in the axis of the trachea. In order to direct the catheter into the left bronchus, the patient's chin and head are turned far to the right.



FIG 8—Roentgenogram showing chin and head turned to right, thereby directing catheter into left bronchial tree

(Fig 8) Each bronchial tree is aspirated dry, the aspiration being applied intermittently to prevent excessive coughing and cyanosis. The catheter is introduced until it reaches the approximate level of the orifice of the lower lobe bronchus, at which time the outer end of the catheter will be about two to three inches from the external nares. If one side shows a greater involvement than the other, the patient may be rolled onto the contralateral side during

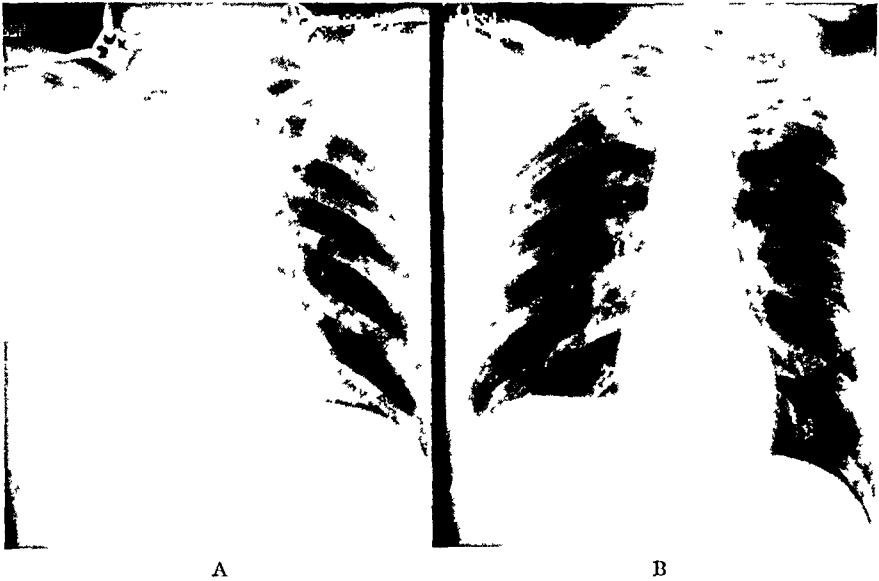


FIG 9—S. B., No. 422071. (A) Roentgenogram 36 hours following bilateral inguinal herniorrhaphy. Atelectasis right lung. Bronchoscopy performed same day because of ineffectual cough and retained bronchial secretions. 25 cc thick mucopurulent secretion aspirated from trachea and right bronchial tree. Cough remained ineffectual. Accordingly, two subsequent aspirations by tracheobronchial suction on same day. Two aspirations by same method on following day until cough became effective. Convalescence satisfactory thereafter. (B) Roentgenogram six days later reveals no pulmonary atelectasis or infiltration.

the aspiration of the more involved lung, so that posture will aid cough in dislodging secretions from the smaller bronchi up to the larger bronchi, where they can be reached by the aspirating catheter. Ordinarily, the procedure of tracheobronchial suction is accompanied by moderate or considerable coughing, which is helpful in raising secretions from the smaller bronchi to the level where they can be removed. It should be emphasized that, unless intermittently applied, the suction will provoke severe coughing and cyanosis, and, accordingly the suction should be used for periods of only several seconds each, the patient being allowed to take a few deep breaths between each period of suction. The total duration of the procedure varies from two to three minutes, depending upon the amount of secretions present. The amount of secretions aspirated is frequently larger than might be anticipated, the average quantity usually being between 10 to 20 cc.

Following the use of bronchoscopy or tracheobronchial suction, voluntary cough usually becomes more effective due to the improved ventilation of the lung beyond the sites of the obstructing secretions. The improved aeration of the lung makes available a larger quantity of air to be displaced by the hehic blast, and peripheral secretions are raised with greater ease. Voluntary

cough, however, may not become completely effective until the patient's general condition improves

As the subsequent formation of secretions is to be expected, the patient should be carefully observed for any evidences of retained secretions, and suction should again be instituted when and if there is further retention of secretions (Fig 9). Owing to the improved bronchial drainage and to chemotherapeutic measures, the accompanying purulent bronchitis subsides and the reformation of secretions gradually lessens. Also, during this interval, the patient's general condition, unless influenced by extrapulmonary complications, gradually improves, and the voluntary cough becomes more effective. The measures mentioned earlier for aiding voluntary cough should be continued, so that voluntary cough will become effective as soon as possible and the need for suction will not be unduly prolonged.

The improvement in the patient's condition following the removal of retained secretions is often striking, especially when the amount of retained secretions may inadvertently have progressed to an alarming degree before recognition. Retained bronchial secretions are obstructing secretions, interfering with the airway to the lungs and preventing adequate ventilation. Accordingly, patients are able to breathe more comfortably following the aspiration of secretions, and cyanosis, if present before the aspiration, will frequently be relieved by the improved pulmonary ventilation. As postoperative atelectasis and bronchopneumonia are usually sequelae of retained secretions, the prompt removal of secretions at the first evidence of their retention will minimize the incidence of these complications and lessen their severity.

SUMMARY

The presence of bronchial secretions, and the decreased pulmonary ventilation and cough efficiency subsequent to operation are vitally important factors in the genesis of postoperative atelectasis and bronchopneumonia. The prompt recognition of retained bronchial secretions is essential in the prevention of these complications, and the methods for eliciting the physical signs of retained secretions are described. The measures for aiding the cough mechanism are discussed and they are frequently effective in providing adequate drainage of the tracheobronchial tree. As retention of bronchial secretions occurs in some instances in spite of these measures, retained secretions should be immediately removed by bronchoscopy or tracheobronchial suction *before* the advanced signs of progressing bronchial obstruction and pulmonary infection have developed. A technic for tracheobronchial suction is described, the simplicity of the technic and its applicability when repeated aspirations are required, merit its more frequent use.

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DISCUSSION —DR ELLIOTT C CUTLER (Boston, Mass.) One of the topics set for discussion at the Stockholm meeting of the International Surgical Society this summer was "Postoperative Pulmonary Complications." I take the contribution of Doctors Ransom and Haight as an evidence of the indestructibility of science at the hands even of totalitarian warfare

If we view postoperative pulmonary complications as a whole, we may find that at least we know something about it, though, since my first studies with Doctor Morton, in 1916, I feel there are still very large gaps. With the advent of local anesthesia, we have evidence that it matters not what the anesthetic is, and the reports from clinics everywhere in the world have come to this point of view. The same pulmonary complications occur under local anesthesia to-day that occurred in 1900 under the hands of Mikulicz, who wrote the first paper on postoperative pulmonary complications under local anesthesia.

If we study the body as a whole, and take fields of surgery and instances of complications in special fields, we learn a great deal. We find that the general percentage of pulmonary complications for all surgery is between 2.5 and 3 per cent, but when we come to the abdomen, it rises to 12 per cent, and when we come to the epigastrium it rises, in some clinics, to as high as 30 per cent. This is of considerable significance, because it must bear some relation, therefore, to the operative field and something that goes on in the operative field.

Having disabused ourselves, therefore, of the idea that the anesthesia plays a role, and having very definite evidence that, apparently, the complications bear a direct relation to the ability of the patient to carry out normal respiration, we have left only one other common factor, which is that these complications occur perhaps 5 to 10 per cent less frequently in females than in males. That has been interpreted by most workers as due to the fact that a man breathes largely with his diaphragm and a woman is a costal respiratory animal.

The proof of these contentions lies in part with adequate studies of vital capacity, and we finished the study of several thousand consecutive surgical operations on whom vital capacity studies have been done daily from the time of admission to the time of discharge, over a period of two and one-half years, and we have had adequate curves of reduction in vital capacity with every surgical procedure.

The reduction varies from a median decrease around 59 to 60 per cent for the epigastrium to practically nothing for the extremities, this correlates, almost exactly, with the incidence of pulmonary complications as a whole.

We felt it was wise to find some remedy for the painful respiration, and sought new drugs and new methods of anesthesia. About the only one that has yielded any benefit is a combination of a long-lasting local anesthetic—eucupin with oil. Under these conditions, eucupin produces anesthesia often lasting for four or five days. In a limited number of patients having upper abdominal incisions, carefully studied by one of my colleagues, we find that, when eucupin is used to block the field, the reduction in vital capacity is about one-half of that in similar patients, similarly operated upon by the same surgeon when eucupin is not employed to block the field.

It seems reasonable to suppose that if an adequate local anesthesia could be found which would render epigastric wounds painless, and respiration would remain normal, we might greatly curtail this disastrous complication for the surgeon.

The authors of this paper have largely restricted their discussion, as we see, to atelectasis. Now, it is difficult to say what the relative frequency of the various clinical forms of pulmonary complications are. If one includes large pulmonary emboli, the pulmonary emboli constitute about 10 to 12 per cent of the complications. Lobar pneumonia, proven by bacterial study, constitutes only 2 or 3 per cent, and you can divide the rest between the clinical diagnosis of atelectasis, either massive or scattered, or bronchial pneumonia. But if you make a clinical diagnosis of scattered atelectasis, and if the patient comes to autopsy, the professor of pathology may tell you it is bronchial pneumonia. Whether that is only because the late stages of atelectasis reach consolidation or not, we do not know.

The chief gift of this paper to-day—and everything has its gift to science—seems to me to be this ingenuous idea of using such a simple method in the wet, blue patient,

as the installation of a catheter into the trachea, and adequate instructions on how to do this have been given. Most of us, I am sure, suck out the mouth, but the addition of tracheal suction will do much.

I have only one other suggestion, which is that if the reduction in vital capacity from pain is an important objective, it is peculiar that all the hibernating animals, from the bear to the bat, do not have this disease, because their respiratory rate is cut down and the vital capacity is almost nothing. So I return again to an old contention of mine—that these complications may result from the promulgation of small emboli up the passageways of the lymphatic current through the pleura of the diaphragm.

DR WALTER ESTLIL LEE (Philadelphia, Pa.) I hesitate to discuss this significant paper because of my too frequent contributions to the subject in the past.

However, such a paper seems timely, for in our experience, and I suspect it is the same with others, the incidence of postoperative atelectasis is increasing. This, of course, may be due, in part at least, to a more general recognition of the condition by both physicians and surgeons, but it seems to us, in most part, to be the result of more radical and more prolonged surgical procedures.

We now speak of six and one-half- and seven-hour operations, such as Doctor Lahey reported recently, and to maintain anesthesia and complete muscular relaxation for such periods of time, spinal, and particularly continuous (intermittent) anesthesia is being employed almost routinely in many clinics. With such a method of anesthesia, most surgeons are using more and more sedatives in the form of morphine, or some type of barbiturate. Under these conditions the respiratory movements are far more shallow than in inhalation anesthesia and the cough reflex is depressed or abolished. Under such conditions it is to be expected that the tracheal and the bronchial secretions will tend to accumulate in the dependent portions of the bronchial tree and even in the alveoli.

One should approach the problem of postoperative atelectasis through prophylaxis rather than by treatment, and though the method which Doctor Haight has outlined is ideal, we would suggest that prophylaxis should start with the anesthetist during the operation, when every effort should be made to maintain, at all times, an unobstructed bronchial airway, and not wait until the close of the operation to start aspiration. This can be done very readily by hyperventilation with oxygen under pressure about every 15 minutes, and if there is any excess of secretion, it should be aspirated during this time, and not wait until the close of the operative procedure.

My appeal is that we should not postpone Doctor Haight's suggestion of tracheal drainage until the signs of bronchial obstruction appear postoperatively, but that routine measures in the form of hyperventilation, with oxygen under pressure, during the operation, and that aspiration of excessive amounts of tracheal secretion at the close of the operation and before the patient leaves the operating table should be practiced routinely.

In our original reports we confessed—probably bragged—that we have performed bronchoscopic drainage in some 80 patients during a period of one year. At the present time, in a much larger group of patients, three to five bronchoscopic drainages a year is our average.

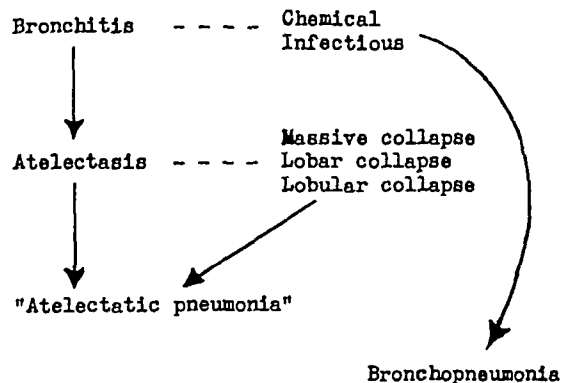


CHART 1

DR FRANK H. LAHEY (Boston, Mass.) I undertake further discussion only because I think this is such an important subject and because it has played such a part in reducing our mortality.

Albert Miller, of Providence, has shown that if you subject people to anesthesia of any type, which is sufficient in depth to produce relaxation, they breathe largely with the diaphragm. Tracings show that most respiration is carried on by the diaphragm whether spinal nitrous oxide

or other anesthesia is used. So, as Doctor Lee has stated, a great deal of our difficulty is probably due to this.

I think we owe a tremendous amount to Chevalier Jackson and Gabriel Tucker because, so long ago, they called our attention to the value of suction bronchoscopy. One has only to see the intrathoracic goiter patients delirious in the middle of the night the secretion sucked out and the temperature down the next day and the patient in a rational state, to realize what an important part this plays in the prevention of pulmonary complications.

Chart 1 is a diagrammatic scheme of the production of these bronchial pneumonias and atelectases. Here is a repetition of what we all have seen, atelectasis so graphically cleared by suction bronchoscopy. Chart 2 shows the temperature and pulse reactions. We could repeat this time after time. There are certain warnings that I think one should note. Our anesthetists should be trained in suction bronchoscopy and, in turn, should train our Fellows in catheter bronchoscopy.

Another point which I think important is that bronchoscopy should be undertaken in the middle of the night, when the condition is discovered, and not at a convenient time the next day. We have demonstrated, in our autopsy findings, how rapidly pneumonitis can develop, and I believe that we should have available the medical men, the roentgenologists, and the suction bronchoscopists to do it, not when it is convenient the next day but whenever the evidence occurs. These patients who have been delirious in the middle of the night, who have had the secretions sucked out and have become conscious and rational, when they have difficulty with their breathing and mucus have even requested its repetition themselves because they have been so much improved. One only has to see the striking results that come from catheter and particularly suction bronchoscopy to be impressed with the fact that this is a real contribution and will, I believe, save many lives. It has played a very important part, I am certain, in making it possible for us to maintain such a low mortality rate in the subtotal gastrectomy cases.

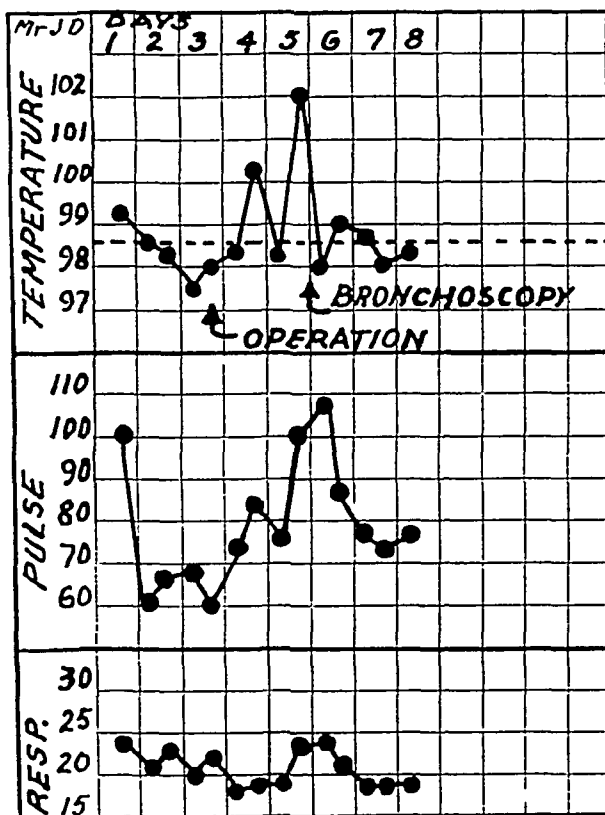


CHART 2

DR HENRY K. RANSOM (Ann Arbor, Mich., closing) I wish to mention briefly two points. First, that conservative measures are of inestimable value in the prevention of postoperative pulmonary complications due to retained bronchial secretions. Such measures include (1) the avoidance of excessive sedation and prolonged periods of semi-consciousness following operation, (2) frequent changes in the position of the patient, (3) encouraging the patient to cough, using carbon dioxide inhalations if necessary, (4) good nursing care, and (5) a cooperative house staff. By attention to these details the process can often be aborted and thus prevented from going on to the more advanced and serious stages. These same measures will also be sufficient in many of the early cases of established atelectasis to afford proper drainage of the bronchial tree, and thereby to effect a cure, and, therefore the more complicated procedures described by Doctor Haight will only occasionally be necessary. Second, during the past several years, transverse incisions have become increasingly popular in the field of abdominal surgery, and especially for operations upon the biliary tract. For the past three years we have employed such incisions and the results have been gratifying. It seems to be true that after healing has taken place the abdominal wall is more sound, that the incidence of incisional hernia is decreased, that patients are more comfortable during the postoperative period, and that they may be allowed out of bed somewhat earlier. We also gained the

impression that there was a lower incidence of pulmonary complications where such incisions were used. Some ten years ago, a similar observation was recorded in an article by Jones and McClure. They stated that in the series of cases reported by them no instances of postoperative pneumonia or atelectasis occurred. We, therefore, reviewed our cases of simple cholecystectomy during the past six years in order to make a comparison of the pulmonary complications noted with vertical and with transverse incisions (Table I).

TABLE I
PULMONARY COMPLICATIONS FOLLOWING CHOLECYSTECTOMY FOR
CHRONIC CHOLECYSTITIS WITH OR WITHOUT CHOLELITHIASIS
1935-1941

Number of cases	Type of Incision	
	Vertical	Transverse
	346	108
Patchy atelectasis or pneumonia	26 (7.5%)	5 (4.6%)
Massive atelectasis	5	0
Pleuritis	1	0
Infarct or embolism	1	1
	<hr/> 33 (9.3%)	<hr/> 6 (5.6%)
Pulmonary complication chief cause of death	3	0
Pulmonary complication contributory cause of death	1	0

These statistics show that while there was a slight decrease in the incidence of pulmonary complications when transverse incisions were used, this decrease was not as great as we had anticipated. Since the number of cases is relatively small, the statistical evidence is not of great significance, but it does suggest that this is one more detail in surgical technic which may be of importance in further reducing the number of these dreaded postoperative complications.

ROENTGEN RAY TREATMENT OF GAS GANGRENE*

CLINICAL AND EXPERIMENTAL OBSERVATIONS

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AT PRESENT, a wave of enthusiasm for roentgen ray treatment of gas gangrene is sweeping the country. This form of treatment was first attempted by Kelly,³ in 1928. By 1933, when his first report appeared, he had treated six cases in this way. Because of this report, others were stimulated to try roentgen ray therapy, and sporadic reports of these cases have appeared in the literature. The dosage of roentgen ray has been standardized to 100 r over the tissues involved with gas gangrene, through two different ports, twice daily, for three days. All of the reports are subject to the same criticism—they fail to consider the level of the lesion on the extremity, the amount of muscle tissue involved and the character and extent of surgical measures employed before or coincidental with the administration of roentgen therapy. Again, it should be emphasized that it is essential to consider whether this form of therapy is the sole cause of fewer deaths and amputations, or whether the surgical and therapeutic measures used at the same time may not be equally beneficial. Since Kelly and Dowell's collected series includes most of the reported cases treated with roentgen ray, and since these authors express the consensus regarding this form of therapy in gas gangrene cases, we will confine our criticisms to their work.

In 1939, Kelly and Dowell⁴ collected 132 cases of gas gangrene treated by roentgen ray, with a mortality of 11.3 per cent. Of these, there were 105 cases of gas gangrene of the extremities (level and extent of the lesions not defined) of which 5.6 per cent were fatal. These did not include the nine cases of diabetic and arteriosclerotic gangrene. An analysis of these cases convinced them that "only the very grave cases will die in spite of x-ray irradiation. Accordingly, treated properly, no case should die of pure gas gangrene but rather from other causes." However, they fail to mention the other measures employed coincidental with roentgen ray treatment and these should naturally influence the evaluation of results.

As illustrative of the ineffectiveness of roentgen therapy the following case from the Charity Hospital of Louisiana is presented.

* Read before the American Surgical Association, White Sulphur Springs, W. Va., April 28, 29, 30, 1941.

Aided by grant from the Schwartz Research Fund

Case 1—R T age 24, received a compound fracture of the right tibia. Twenty-four hours after injury clinical signs of gas gangrene appeared. Incisions, standard roentgen ray therapy for three days, sulfanilamide and serum were employed, but diffusion of the infection was not arrested. A guillotine amputation above the knee was then performed, four days after injury. After amputation, there was no progress of the infection although no special measures were employed.

Further examples of clinical cases which were not benefited by roentgen therapy can be found in the literature. Cubbins, *et al*,¹ stated that all eight patients with proved gas infection treated with roentgen ray and without surgery or antitoxin, died. Coleman and Bennett² reported treating 14 cases with roentgen ray alone with four recoveries and 10 deaths. However, according to these two observers, in the four cases which responded to roentgen ray, wide opening and amputation were responsible for recovery.

Kelly and Dowell³ believe that amputation is absolutely unnecessary. In support of this view they present a series of 17 cases of "therapeutic amputation," with a mortality of 11.7 per cent. These are compared with 72 other cases of gas gangrene of the extremities treated with roentgen ray but not amputated, with a mortality of 4 per cent. Surgical and medical measures carried out coincidentally are carefully omitted, the interval from onset of symptoms of gangrene until amputation was performed is not mentioned, the level and extent of involvement are not discussed and the degree of toxemia or shock at the time amputation was performed is not given. Any or all of these factors, necessarily, are more responsible for death or survival of the patient than the effect of roentgen ray treatment. It is not fair to ignore the commonest causes of death and consider only one form of therapy in relation to mortality. As further evidence of the uselessness of amputation, they³ state: "The fact that some of these patients still showed gas in the tissues above the site of amputation, but recovered under x-ray treatment is convincing evidence of its therapeutic value. Accordingly it would seem that those patients lost an extremity unnecessarily inasmuch as they still had the disease after the amputation. Their ultimate recovery can only be attributed to some cause other than amputation." No surgeon can fail to recognize the fact that when the small muscles of the foot alone are involved with gas gangrene, amputation at or immediately above the ankle joint will arrest the progress of the infection and cure the patient, or that when the disease is entirely below the knee joint, disarticulation at the knee or guillotine amputation above the knee will certainly save the patient's life. Surgeons, with adequate experience, can invariably recall instances in which guillotine amputation was performed through discolored muscles, with gas in the subcutaneous tissues. In many of these cases when the stump was left wide open and the fascia and skin split for some distance above the level of amputation, complete recovery followed without the benefit of roentgen ray therapy or serum.

Not only does Kelly believe that amputation is a useless therapeutic procedure but he and his coworkers,⁵ in 1938, stated "Severe debridement

measures are no longer justifiable" since "early and frequent treatment with small doses of x-ray is the answer to the question of what to do to prevent or to treat an infection with gas-forming organisms"⁴ The following case from the Charity Hospital illustrates the fallacy of this statement

Case 2—J H, age 35, received a compound fracture of the left tibia Within 36 hours of injury, signs of gas gangrene appeared About 12 hours after the first evidence of gas gangrene was noted, the previous laceration was opened widely, the incision extended upward and downward, and a large amount of necrotic muscle was removed and drainage instituted The lesion was irrigated with hydrogen peroxide and sulfanilamide was given Although no roentgen therapy was administered at any time, the infection was arrested and the patient subsequently recovered

These clinical observations serve to emphasize the rationale of the surgical treatment of gas gangrene, since it meets the bacteriologic and pathologic indications Roentgen ray therapy, obviously, cannot and will not achieve this end

The use of roentgen ray therapy in the treatment of gas gangrene is purely empirical Faust⁷ suggests as a possible explanation of the action of roentgen ray "Recently three Stanford University zoologists have reported that x-rays played upon nutrient fluids are deadly to protozoa by producing small quantities of hydrogen peroxide" A review of this report by Taylor, *et al*,⁸ reveals that they employed 38,400 r on these nutrient fluids to obtain the lethal effect on protozoa Such massive dosage is not therapeutically possible in the treatment of human beings Moreover, it is hardly fair to conclude from their experiments that because with large doses of roentgen ray certain protozoa are destroyed in a sterile yeast medium, anaerobic bacteria can be killed in human tissue by very small doses of roentgen ray

Very little experimental work has been done to evaluate, scientifically the effect of roentgen ray in the treatment of gas gangrene Kelly and Dowell⁶ attempted some experimental work but they state "We could not determine anything to our satisfaction, as it seemed to us that the pig is too small an animal to inject with the virulent gas gangrene and then attempt to cure it with the x-rays If a real active strain of gas bacillus organisms were used it traveled so rapidly that it was soon necessary to treat most of the pig and the combination of general body irradiation left too much undecided Some pigs got well and some died and in the end we determined nothing" We have not encountered this difficulty in our experimental work

Description of Experiments—Gunea-pigs, averaging 16 to 18 ounces in weight, were anesthetized with ether An incision was then made over the lateral aspect of the left thigh to expose the shaft of the femur The muscle layers were split in order to produce approximately the same amount of muscle damage with each individual exposure of the shaft of the femur With a fine motor-driven drill, two holes were made through the outer cortex of the femur, thereby opening the marrow cavity This procedure was an at-

tempt in order to reproduce, artificially, a compound fracture without using a splint. A portion of 0.15 cc of an 18- to 20-hour broth culture of *Clostridium welchii*, a minimal lethal dose, was then placed in the wound, which was closed with interrupted sutures.

The purpose of these experiments was to determine the effect of various chemical and physical agents in preventing the development of gas gangrene in these wounds. The present communication is confined to a comparison of surgical treatment alone with roentgen ray therapy. Exposing these animals to therapy within one hour of inoculation is not in our opinion comparable to treating fully developed gas gangrene. We feel, therefore, that we may, validly, draw some conclusions from these experiments regarding the benefit of surgery and roentgen ray as measures which will control the development of the disease. It was arbitrarily decided to test each individual procedure one hour after inoculation. By this time there was no definite swelling, no gas in the tissues, no discoloration nor loss of contractility of the muscles. The only clinical evidences of infection were slight edema and sero-sanguineous discharge. A group of 58 animals, with closed wounds, was used as controls throughout the course of the experiment. This group not only gave information regarding the average death time but also insured the continued potency of the organism.

During the whole period of observation, there were about 400 animals operated upon, inoculated, and treated with various agents. It was observed that any animal that lived 72 hours or more did not die as a direct result of gas gangrene. Secondary infection, general sepsis, or complications such as pneumonia were the principal causes of death in animals living beyond this period. In compiling and tabulating the results with reference to gas gangrene, it was decided to consider as survivals all animals living beyond 72 hours. The "average death time" represents an average of the number of hours the animals that were not included in the survivals lived.

Ten animals were treated by simple incision alone, one hour following inoculation. A group of 20 animals were extensively debrided without any further therapy, one hour after inoculation. Forty animals were used in four experiments, in an effort to determine the approximate effective dosage of roentgen ray. From these experiments, it was found that the smaller doses of roentgen ray had a more beneficial effect. Therefore, a standard dosage of 25 r at 7 Ma, 100 Kv, 21 cm distance, no filter, with a uniform size port was arbitrarily used. The first group of animals studied received this dosage of roentgen ray alone, one hour after inoculation. A similar group was studied in which the same dosage of roentgen ray was combined with simple incision of the wound. A third group received roentgen ray and extensive surgical debridement.

We, therefore, have a group of animals with closed wounds as controls to compare with the group receiving roentgen ray alone, a group with simple incision to compare with those having incision and roentgen ray, and, finally,

a group with débridement alone as compared with débridement and roentgen therapy

GROUP I

Control Series—58 Animals

The wounds were exposed and inoculated as described. Following inoculations, the wounds were closed tightly with interrupted sutures. Nothing further was done. Eight in the group survived. In all the animals there was definite clinical evidence of gas gangrene. The survivals might be explained on the basis of two factors. (1) It was impossible to keep some of the animals from chewing the wounds open, thus producing an open wound and thereby lessening the possibility of spread of the infection. (2) Certain animals had a natural resistance to the disease, permitting them to control the spread of the infection. The most interesting feature of the control group, however, is that all the animals showed definite signs of gas gangrene at some time during the observation period. As will be noted in the tables, the average death time for the whole group was 27.7 hours. However, this figure is slightly misleading, since 69 per cent of all the animals died in less than 36 hours, and fully 80 per cent of all the group died as the result of an active gas gangrene. Those animals with active gas gangrene showed extensive involvement of the thigh musculature extending up into the abdominal wall, with lysis of the muscle tissue, a profuse serosanguineous discharge, crepitation in the soft tissues, and a very distinct characteristic odor. Those wounds which were opened by the animal or which opened spontaneously, inevitably became secondarily infected, but no studies of the various strains of contaminating organisms was made.

TABLE I

CONTROL GROUP—CLOSED WOUNDS

Number of animals	58
Average death time	27.7 hours
Survivals (over 72 hours)	8
Animals with definite gas gangrene	58
Animals dying as direct result of G. G.	48
Animals dying of other causes	2

GROUP II

Simple Incision—22 Animals

The compound fracture was produced as described. Following inoculation, the wounds were tightly closed and allowed to remain so for one hour. Then the wounds were opened widely. The skin incision being enlarged to approximately twice its original size, the wound was irrigated with saline in some instances and tap water in others, and then allowed to remain open. No difference could be found in the effect of the agents used for irrigation. The average death time was 32.8 hours, a definite improvement over the control series. Four animals in the group lived. Again, all the animals showed clinical evidence of gas gangrene at some time during the observation period,

and 18 of the 22 (82 per cent) animals died as a direct result of the gas gangrene infection. Simply opening the wound at the end of one hour did not stop the development of gas gangrene, but was of some benefit in helping to combat the infection.

TABLE II

SIMPLE INCISION

Number of animals	22
Average death time	32 8 hours
Survival (over 72 hours)	4
Animals developing gas gangrene	22
Animals dying as direct result of G G	19

GROUP III

Surgical Débridement—20 Animals

The wounds were exposed and inoculated as described. Following inoculation, the wounds were tightly closed and allowed to remain so for one hour. At the end of this time, the wounds were opened widely, and all traumatized and devitalized muscle tissue was completely excised. No fragments of muscle sectioned transversely were allowed to remain. The whole lateral aspect of the femur was exposed and, because of the loss of support, the femur fractured with very little trauma. Wherever the femur was broken through completely, the chance for development of active gas gangrene was increased and the chance for actual survival practically nil.

In this group, the average death period was 63 1 hours. The most important observation was that only four animals had extensive clinical gas gangrene and two others showed local evidence without spread into the abdomen. Thus, in only six of the 20 animals did gas gangrene develop. The remaining 14 animals failed to show any evidence of active infection at any time. The importance of the additional soft tissue trauma caused by the presence of a fractured femur must again be emphasized.

TABLE III

SURGICAL DÉBRIDEMENT

Number of animals	20
Average death time	63 1 hours
Survivals (over 72 hours)	14
Animals with definite gas gangrene	6
Animals dying as direct result of G G	4
Animals dying of other causes	2

ROENTGEN PHASE

Before undertaking any experiments employing roentgen therapy, 40 animals were chosen and, in groups of ten, exposed to varying dosages of roentgen ray, one hour after the usual wound preparation and inoculation. All wounds were allowed to remain closed. All constant factors remained the same, a uniform size port being used throughout every experiment, and the therapy machine adjusted at 100 Kv, 7 Ma, 21 cm distance, with no filter. Dosages of 35 r, 100 r, 150 r, and 400 r were administered to each of four

groups respectively. In no instance was the development of gas gangrene prevented, although those animals receiving the smaller doses of roentgen ray did seem to do much better than those receiving the larger doses. This finding agrees with the clinical observations of many authorities. It was, therefore, decided to use a dosage of 25 r in the remainder of the experiments.

GROUP IV

Roentgen Ray with Closed Wounds—20 Animals

The wounds were exposed and inoculated, after which they were tightly sutured. One hour after inoculation the animals were given 25 r (100 Kv—21 cm—7 Ma—no filter). The average death time for the group was 29.9 hours. Every animal in the group had gas gangrene, and all died as a result of the infection. Fifteen of the animals died within 36 hours, and all animals within 48 hours.

TABLE IV

ROENTGEN RAY WITH CLOSED WOUNDS

Number of animals	20
Average death time	29.9 hours
Survivals (over 72 hours)	0
Animals with definite gas gangrene	20
Animals dying as direct result of G. G.	20

No doubt, if a sufficiently large series of animals were studied there would have been some survivals. However, their absence does not, we believe, detract from the main fact that all animals developed gangrene, and that the average death time was only slightly above that of the control group, suggesting that any effect from roentgen ray alone was minimal.

GROUP V

Roentgen Ray with Simple Incision—20 Animals

In ten animals, the marrow cavity of the femur was opened. In ten animals, no drill holes were made into the marrow cavity. Otherwise the inoculation and preparation of the wounds were identical. All wounds were closed for one hour with interrupted sutures, after which the thigh was treated with 25 r (100 Kv—21 cm—7 Ma—no filter). Immediately thereafter, the wounds were widely opened and the fascial layers incised down to the femur.

The average death time for this group was 39.3 hours. Though gas gangrene developed in every animal in the group, still the survival period was definitely prolonged. It seemed as though the roentgen ray therapy had some slight effect in retarding the spread of infection but certainly not in preventing its development.

TABLE V

ROENTGEN RAY WITH SIMPLE INCISION

Number of animals	20
Average death time	39.3 hours
Survivals (over 72 hours)	5
Animals with definite gas gangrene	16
Animals dying as direct result of G. G.	14
Animals dying of other causes	1

GROUP VI

Roentgen Ray with Débridement—30 Animals

The animals were prepared as previously described. The wounds were closed tightly for one hour. The thigh was then exposed to 25 r (100 Kv—21 cm—7 Ma—no filter). Immediately thereafter, the animals were again operated upon and all devitalized and traumatized muscle was radically debrided.

The average death time for the group was 60.4 hours. Again, the striking feature was that in the majority of the animals gas gangrene failed to develop. Only six of the 30 animals had definite evidence of gas gangrene in their wounds at the time of death. Postmortem examination revealed definite gas bubbles in all six animals. The administration of roentgen ray also required that the animals be handled and tied to animal boards an extra time. Therefore, in this group fracture of the femur occurred more than when only débridement was undertaken. If the muscle tissue remained firm and reddish in color, even though gross secondary infection was present, we did not feel that the animals had succumbed primarily because of gas gangrene.

TABLE VI

ROENTGEN RAY WITH DÉBRIDEMENT

Number of animals	30
Average death time	60.4 hours
Survivals (over 72 hours)	14
Animals with definite gas gangrene	6
Animals dying as direct result of G. G.	6
Animals dying of other causes	10

Discussion—It may seem, at first, that the control group is unnecessarily large and that this would necessarily alter the statistics, since all other groups were much smaller. This series of experiments represents only a portion of a much larger series in which the effect of various chemical agents have also been studied. Over a period of seven months, whenever ten animals were studied, a group of two to three animals were included in which the wounds were kept closed. The control group, therefore, represents a true average of the death time over this whole period and insures the constant virulence of the organism used and the ability on our part of consistently reproducing gas gangrene experimentally in guinea-pigs.

In comparing Group I with Group IV, that is, the control group with those animals whose wounds were allowed to remain closed and then exposed to 25 r dosage of roentgen ray, it will immediately become apparent that the roentgen ray given did not prevent the development of gangrene in any instance. There is apparently some minor effect attributable to the roentgen ray therapy inasmuch as the average animal did not die as quickly, but this figure may not be as significant as it appears at first glance. In the control group, the average death time was 27.7 hours, in the comparable roentgen ray group, 29.9 hours. The most significant observation, in our opinion, was that every animal in both groups manifested definite clinical evidence of gas gangrene.

From a comparison of Groups II and V, that is, the group with simple incision and that with simple incision supplemented by radiation, a bit more evidence as to the efficacy of roentgen ray therapy may be inferred. This fact is not borne out by the average death time (32.8, Group I, 39, Group V) as much as by the fact that four of the 20 animals given roentgen ray failed to contract gas gangrene whereas every one of the 22 animals having surgery alone did. It may be stated, therefore, that roentgen ray has some beneficial effect as a prophylactic measure, but it must also be remembered that this effect of roentgen ray may be more apparent than real, since it is not borne out by a comparison of Groups III and VI.

A comparison of Group III and Group VI shows, immediately, the value of early debridement as a prophylactic measure. Even though vegetative forms of a virulent strain of *Clostridium welchii* were placed in a bed of traumatized tissue, and allowed to incubate there for one hour, it still was possible to stop completely the development of gangrene in 80 per cent of the animals of both groups. The addition of roentgen ray did not improve the results obtained in Group VI.

TABLE VII

RESULTS

Group	Treatment	Animals	A D T	Surv	Dev G G	Died G G	Other Deaths
I	Closed w ds	58	27.7 hr	8	58	48	2
IV	Closed w ds and x ray	20	29.9 hr	0	20	20	0
II	Incision	22	32.8 hr	4	22	18	0
V	Incision and x-ray	20	39.0 hr	5	16	14	1
III	Débridement	20	63.1 hr	14	6	4	2
VI	Débridement and x ray	30	60.4 hr	14	6	6	10

We may conclude, therefore, that as a prophylactic measure roentgen ray alone has no real effect, that it may be of some value as an adjunct to surgery, but certainly can never be substituted for it.

SUMMARY AND CONCLUSIONS

(1) Clinical reports of the fewer amputations and lower mortality rate in gas gangrene as a result of the administration of roentgen ray therapy, which have thus far appeared in the English literature, have been analyzed and found subject to criticism. They fail to consider all the factors concerned, since they omit the most important and probable causes of death, on the one hand, and the known benefits of concomitant surgical measures, on the other.

(2) A case is cited directly refuting assertions made by some of the authors concerning the efficacy of roentgen ray therapy.

(3) A case is presented as illustrative of the value of radical excision of muscles under certain conditions.

(4) Experimental work on guinea-pigs is reported. The results emphasize the value of early débridement in the control of gas gangrene, but fail to show more than slight improvement from roentgen ray therapy.

(5) Earlier and better surgical measures continue to offer the best means of preventing and controlling gas gangrene

Explanation of abbreviations used in tables

G G—Gas gangrene

W'ds—Wounds

A D T—Average death time

Surv—Survival

Dev—Development

X-ray—Roentgen ray

The kind assistance of Dr Manual Garcia, Assistant Radiologist in Charge of Therapy, Charity Hospital, New Orleans, La, is gladly acknowledged and greatly appreciated

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DISCUSSION—DR FRANK L MELENEY (New York, N Y) I have followed Doctor Caldwell's work closely for some time, and would like to say a few words about what the subcommittee on Surgical Infections, of the National Research Council, has done in regard to this subject

It is true that the literature which has appeared has been based on insufficient, insecure, and often unreliable data However, most of the reports have been favorable The two which Doctor Caldwell quoted were unfavorable, but the great majority have indicated a clinical impression that roentgenotherapy has been of value in the treatment of gas gangrene

However, our committee was not satisfied with the data as they appeared, and we asked Doctor Kelly to reassemble his material in order to answer seven questions which we put to him, and which we thought were significant He did so, and the data which he then submitted to us seemed to indicate that we will have to give careful experimental consideration to this method of treatment Certain statistics which he has assembled, not only from his own work but from the reports that have appeared in the literature, I would like to quote In a total of 364 cases, which includes his own as well as those of others that have been reported, the mortality is 11.5 per cent In those cases in which only a clinical diagnosis was made, without bacteriologic or roentgenologic evidence, the mortality was 17.2 per cent Where the diagnosis was indicated by the presence of gas in the tissue, without bacteriologic control, the mortality was 17 per cent, and in

those cases in which the diagnosis was confirmed by bacteriologic examination, it was only 86 per cent

In reviewing all of the cases, it seems likely that most of them were really gas gangrene and that the mortality has been materially reduced, in that series at least, by the use of irradiation, in addition to other methods

In Doctor Caldwell's experimental work it certainly seems as if he has demonstrated that with these guinea-pig infections roentgenotherapy was of no value whatsoever. Yet I do not feel that we can carry over the results of animal experiments to human cases, particularly with small animals. One reason is that the irradiation has to be given over a large proportion of the body surface and may, of itself, be injurious. Other workers have had similar results as far as guinea-pigs were concerned, but in dogs, it has been demonstrated that roentgenotherapy has been more successful in decreasing the mortality.

We think that all of these different methods of treatment for the prevention and cure of infection in contaminated wounds have to be subjected to an extensive and well-controlled clinical experiment. This has been planned by the subcommittee on Surgical Infections. This plan is recorded in one of the papers which is read by title at this meeting. We are now waiting for adequate financial support to carry that plan through. It is based upon a complete bacteriologic analysis of all of the wounds which we propose studying—burns, badly lacerated, contaminated wounds, and compound fractures—with categories to include those methods of treatment that seem most likely to give favorable results. Among these are irradiation and the newer chemotherapeutic agents. We trust that at the end of the study we will be able to answer this question, which, as our president said, must be solved in the course of time. We hope that by this plan we can solve it in a relatively short period of time.

DR PHILIP D. WILSON (New York, N. Y.) There are just two little points that I thought might be of interest in regard to gas infection, that I learned in England. The first is in regard to debridement. That not only in debridements in general, but particularly in cases of gas infection, it is too often forgotten that the blood supply of the long muscles enters at the upper end and that, therefore, when debridement is undertaken in the center of muscle the distal portion of the muscle should also be removed.

The second was in reference to the studies of sulfathiazole or chemotherapy in the treatment of gas infection, two independent groups of workers in England reported practically identical conclusions. That sulfanilamide had practically no effect on the control of gas infection, that sulfapyridine was without effect likewise, but that sulfathiazole very definitely did have effect, and that the best results were obtained by the combined use of serum and sulfathiazole.

CONSERVATIVE AMPUTATION OF GANGRENOUS PARTS BY CHEMOSURGERY*†

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THE CHEMOSURGICAL TREATMENT of gangrene is an outgrowth of the chemosurgical method for the microscopically controlled removal of accessible cancers¹ In the course of the cancer investigations, it was observed that following the separation of the tissues which had been chemically killed and fixed *in situ, i e*, on the body of the patient, there developed an exceptionally healthy, highly vascular, germ-resistant area of granulations which supported the rapid ingrowth of epithelium and led to healing with a remarkably healthy, smooth, pliable scar The idea that this excellent healing might be used to advantage in the conservative amputation of gangrenous parts led to the present investigations

Technic—The technic of the chemosurgical treatment of gangrene involves First, the chemical fixation of the gangrenous part, and, second, the surgical excision of all but a thin layer of the tissue thus fixed A number of fixative chemicals have been used but zinc chloride has been the most satisfactory This chemical is incorporated in a concentration of about 40 per cent in a special plastic base²

The steps in the technic may be illustrated by the accompanying diagram showing a gangrenous great toe and a gangrenous sinus which extends several centimeters up along the flexor tendon sheath (Fig 1) The first step is to render the surface keratin permeable to zinc chloride by applying a keratolytic such as dichloroacetic acid The zinc chloride paste is then applied to the toe in a layer 2 Mm thick, in order to fix the toe to a level somewhat proximal to the limits of the visible gangrene The material is held in place by a cotton dressing, and excessive drying is avoided by covering with a second layer of cotton, spread with vaseline Although usually unnecessary, orders are written for analgesics to be given as required

After about 24 hours, the entire toe has been fixed and can be amputated with a scalpel and bone rongeur (Fig 1 A) Since only fixed tissue is incised, there is no pain or bleeding from this procedure unless the incision is inadvertently carried into living tissue If bleeders are encountered, they are

* Read in part before the American Surgical Association, White Sulphur Springs, W Va, April 30, 1941

† This project was aided by the Thomas E Brittingham Fund, the Jonathan Bowman Memorial Fund and the Wisconsin Alumni Research Foundation

coagulated by applying small squares of fixative-impregnated gauze under momentary pressure

If the cut-surface presents an area of soft grayish tissue (Fig 1 B) it is necessary to carry fixation farther. Often gangrenous sinuses extend some distance up along the tendon sheaths, periosteum and other structures. Fixation and excision is repeated until a gangrene-free saucerized area results (Fig 1 A, level of amputation at three days). Then sterile vaselined gauze

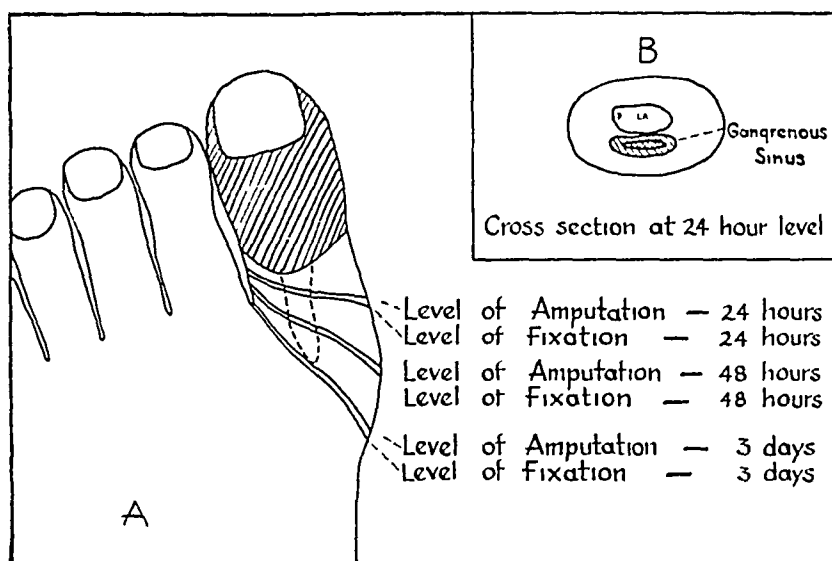


FIG 1—Diagram showing the technic for the chemosurgical amputation of a gangrenous toe. (A) Dorsal view. The shaded area represents the visible gangrene. The dotted line indicates the location of a deep gangrenous sinus. Notice that the level of amputation at each 24 hour interval is just distal to the level of fixation, thus incisions are made only through fixed tissue. Also notice the way in which the wound is kept saucerized. (B) Cross section at the level of amputation at 24 hours. The gangrenous sinus, which in this example followed along a tendon sheath, is easily distinguished by its softness and darker color from the surrounding nongangrenous tissue which in the fixed state is firm and grayish white.

dressings or warm compresses are applied, and separation of the thin final layer of fixed tissue is awaited. In favorable cases, most of this layer can be removed after a week or ten days. The bone is left for another week or so to allow a line of demarcation to form between the fixed and unfixed bone. Adhesions are allowed to form around tendons so when they are cut they will not retract into their sheaths—forming sinuses which may cause recurrence of infection and gangrene. Bettman's' scarlet red-oxyquinoline sulphate gauze is used to promote healing and to prevent infection. The patient may walk around during healing.

Results—Of a total of 66 gangrenous extremities, occurring in 60 patients, healing occurred in 40, or 60.6 per cent (Table I). In diabetic gangrene the results were better than in plain senile arteriosclerotic gangrene. Thus, in 58 cases of diabetic gangrene healing occurred in 63.8 per cent, while in six cases of arteriosclerotic gangrene healing occurred in only 33.3 per cent. One case of gangrene, in a case of Buerger's disease, was nearly healed when the patient developed an acute recurrence of circulatory impairment, the ulcer widened and became so painful that the leg was amputated, though the gangrene did

not reappear. One case of frost-bite gangrene involving the tips of four toes responded well.

Of the 26 unsuccessful results ten were due to failure of the basal layer of fixed tissue to separate. In six, there was extension of the gangrene, in one, extension of purulent infection, and in one, extension of gas bacillus infection. Four signed their release and four died of intercurrent diseases before healing occurred.

TABLE I
RESULTS OF CONSERVATIVE CHEMOSURGICAL AMPUTATION IN GANGRENE
OF VARIOUS ETIOLOGIC TYPES

Etiology of Gangrene	No of Lesions	No Healed	Per Cent Healed
Diabetic arteriosclerosis	58	37	63.8
Senile arteriosclerosis	6	2	33.3
Thrombo-angitis obliterans	1	0	0
Frost bite	1	1	100.0
Total all types	66	40	60.6

It should be pointed out that these statistics refer to an essentially unselected group of cases in which a number of obviously poor subjects were included, and that the cases treated during the developmental period are included as well as those treated after the technic was perfected.

There were no deaths attributable to the procedure in this series, and in no instance was there a breakdown of the scar once healing had occurred, even though gangrene might occur elsewhere on the same or opposite extremity.

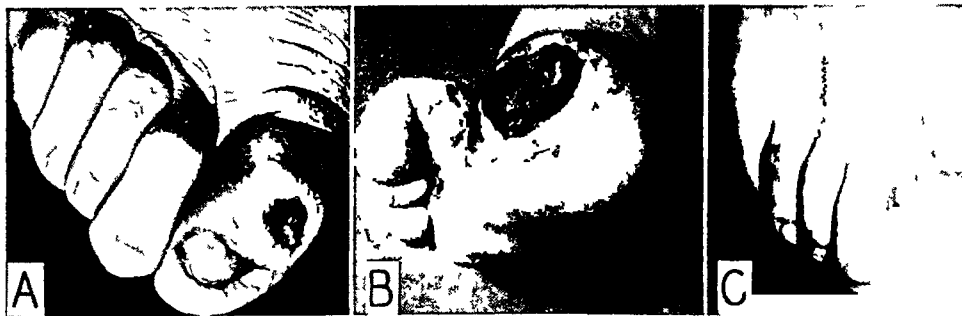


FIG. 2.—Case 1. Diabetic gangrene of right great toe. (A) Before chemosurgery. (B) Ten days later showing excellent granulations. (C) Six months later showing healthy scar.

The following case reports illustrate the results of chemosurgery in some of the commonly-met forms of gangrene.

CASE REPORTS

Case 1—F. W., male, age 57, diabetic. Four months before admission the left great toe had been "burned" by kerosene which had been spilled on a felt slipper. The resulting sore failed to heal despite warm compresses. Soft gangrenous tissue, purulent exudate, and spicules of bone were observed in the deep ulcer (Fig. 2 A). The diseased tissue was fairly well-demarcated from the surrounding tissues, which showed a moderate amount of inflammatory reaction. The dorsalis pedis and posterior tibial pulsations were moderately strong. Chemosurgical amputation was complete in three days. Seven days later the basal layer was removed, revealing excellent granulation tissue (Fig. 2 B).

Healing was uneventful and a healthy scar was observed on a check-up visit six months later (Fig 2 C)

Case 2—D M, male, age 73, with senile arteriosclerosis, no diabetes. For one year prior to admission the left fourth toe had been more or less inflamed and painful. During the past three months the entire toe had become gangrenous despite conservative treatment with warm compresses at another hospital. The junction between the gangrenous and living tissues was fairly well-defined, and there was a copious, odoriferous, purulent exudate (Fig 3 A). The adjacent tissues were slightly inflamed.

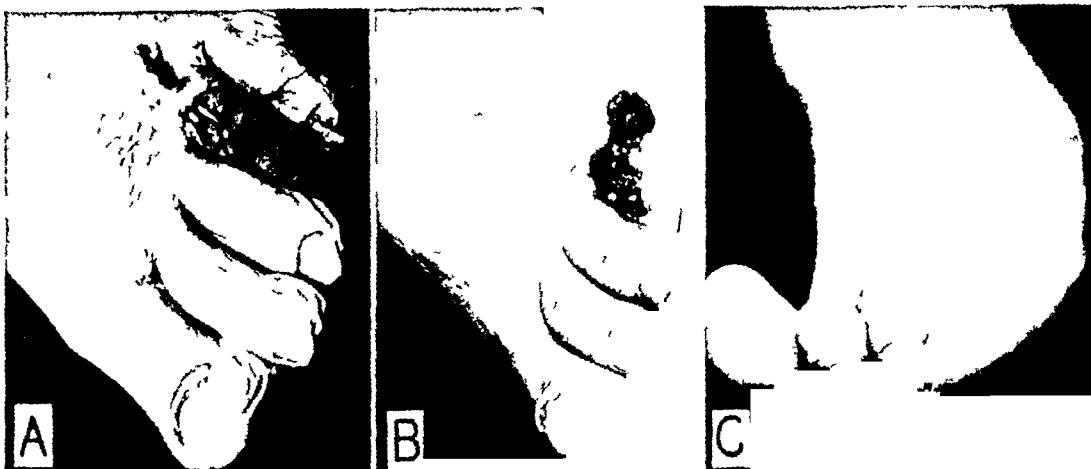


FIG 3—Case 2. Senile arteriosclerotic gangrene of the left fourth toe. (A) Before chemosurgery. (B) Twenty-four days later, showing skin growing across granulation tissue. (C) Three months later, showing excellent scar.

Four days were required for chemosurgical removal of the gangrenous toe and a sinus which extended into the dorsum of the foot. The fifth toe was also amputated, since its blood supply could not be preserved. The basal layer of fixed tissue was removed 12 days later, and in another six days the fixed bone was removed. By the twenty-fourth day, the granulations were excellent and epithelization was progressing rapidly (Fig 3 B). A healthy scar resulted (Fig 3 C).

Case 3—C C, female, age 58, diabetic. Six weeks before admission a sore developed at the base of the left fourth toe which became red and swollen. Bone destruction caused the toe to become shortened and flabby. Five days before admission the second toe suddenly turned black. Midhigh amputation was advised but was refused by the patient. Copious, foul, sanguino-purulent material exuded from sinuses at the base of the toes. The entire foot was red and swollen (Fig 4 A).

The viable third and fifth as well as the gangrenous second and fourth toes were chemosurgically amputated because the infected gangrenous sinuses involved the bases of all toes except the first. Five days were required for removal of the affected tissues because the copious exudate diluted the fixative chemical. Warm compresses were applied and in 12 days the basal layer had separated. Healing was uneventful and the result was a usable foot (Fig 4 B).

Case 4—C M, male, age 57, diabetic. One month before admission the left foot began to swell, and in one week it ruptured over the ball of the foot, draining large amounts of pus. Despite boric acid compresses, incisions, and Dakin's irrigations, the sinuses extended back to the heel and through the foot to the base of the fourth and fifth toes on the dorsal surface. The third toe had recently become gangrenous (Fig 5 A and B). The affected tissues were only fairly well-demarcated from the surrounding tissues but the inflammatory reaction was marked. The dorsalis pedis and posterior tibial pulsations were moderately strong. There was a fairly good histamine wheal reaction on the dorsum of the left foot.

The lateral three toes were amputated by the fourth day, and the walls of the gan-

grenous sinuses treated by inserting gauze, impregnated with the fixative, to prevent the chemical from being washed out by the exudate. By the fifteenth day, the basal layer of fixed tissue had separated on the dorsum, and a few days later the plugs of fixed tissue were removed from the sinuses (Fig 5 C and D). The sinuses were collapsed by pres-

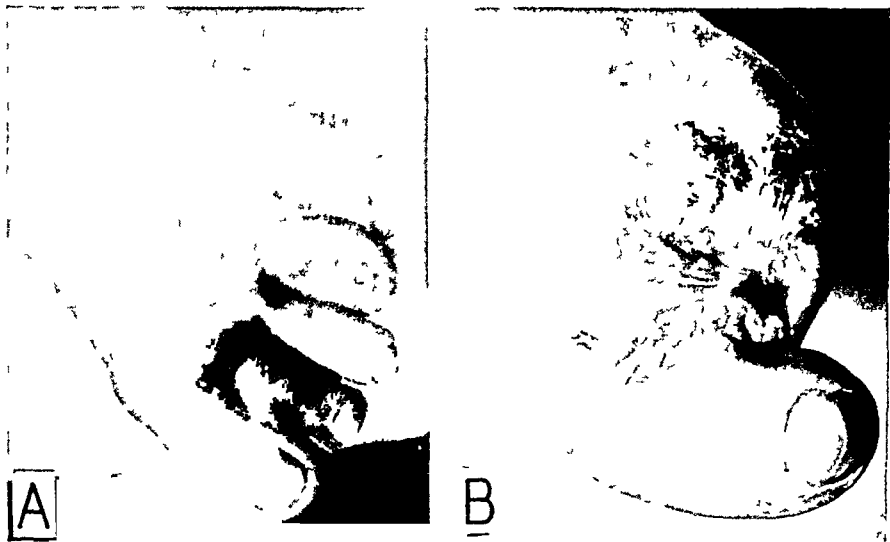


FIG 4—Case 3. Diabetic gangrene of the left second and fourth toes with gangrenous sinuses at bases of all but the great toe. (A) Before chemosurgery. (B) Eleven months later, showing usable foot.

sure-dressings so the walls healed together. By this means, it was possible to preserve a good bearing surface, enabling the patient to walk any distance without discomfort (Fig 5 E and F).

Case 5—K. P., female, age 74, diabetic. Six weeks before admission the patient had removed a callus from the plantar surface of the right great toe. This toe became swollen and painful. Despite conservative treatment in the hospital with warm compresses, incisions, and Dakin's solution irrigations, the plantar and medial surface of the great toe became gangrenous and the entire anterior part of the foot became riddled with gangrenous sinuses. A small area of gangrene also developed on the dorsum of the foot (Fig 6 A). The gangrenous areas were fairly well-demarcated from the surrounding tissue and the inflammatory reaction was marked. The dorsalis pedis pulsation was strong.

Refusing the advised midhigh amputation, the patient consented to chemosurgical treatment. The anterior part of the foot was removed in nine days. Large pockets filled with pus and gangrenous material were encountered. At the end of two months the basal layer of fixed tissue, including the bone, had separated and healing was well under way (Fig 6 B). At a check-up visit, ten months later, the stump had healed well (Fig 6 C) and the patient could walk on the foot, with only a slight limp.

Prediction of Outcome—In order to determine what factors are most important in predicting the outcome of chemosurgical amputation in a given case, all referred cases were accepted for chemosurgery, whether or not it was thought that healing would occur.

The more significant prognostic criteria are summarized as follows:

(1) Diabetic gangrene has a better prognosis than the senile arteriosclerotic type. Doubtless, the difference depends largely upon the predominant influence of infection in most cases of diabetic gangrene as contrasted

with the predominant influence of ischemia in most cases of arteriosclerotic gangrene

(2) The younger the patient, the better the prognosis

(3) The more definite the demarcation between the gangrenous tissue and the living tissue the better the chances for healing

(4) The greater the reaction of the living tissues to the gangrenous tissue, as indicated by redness, swelling, heat and purulent exudation, the better the

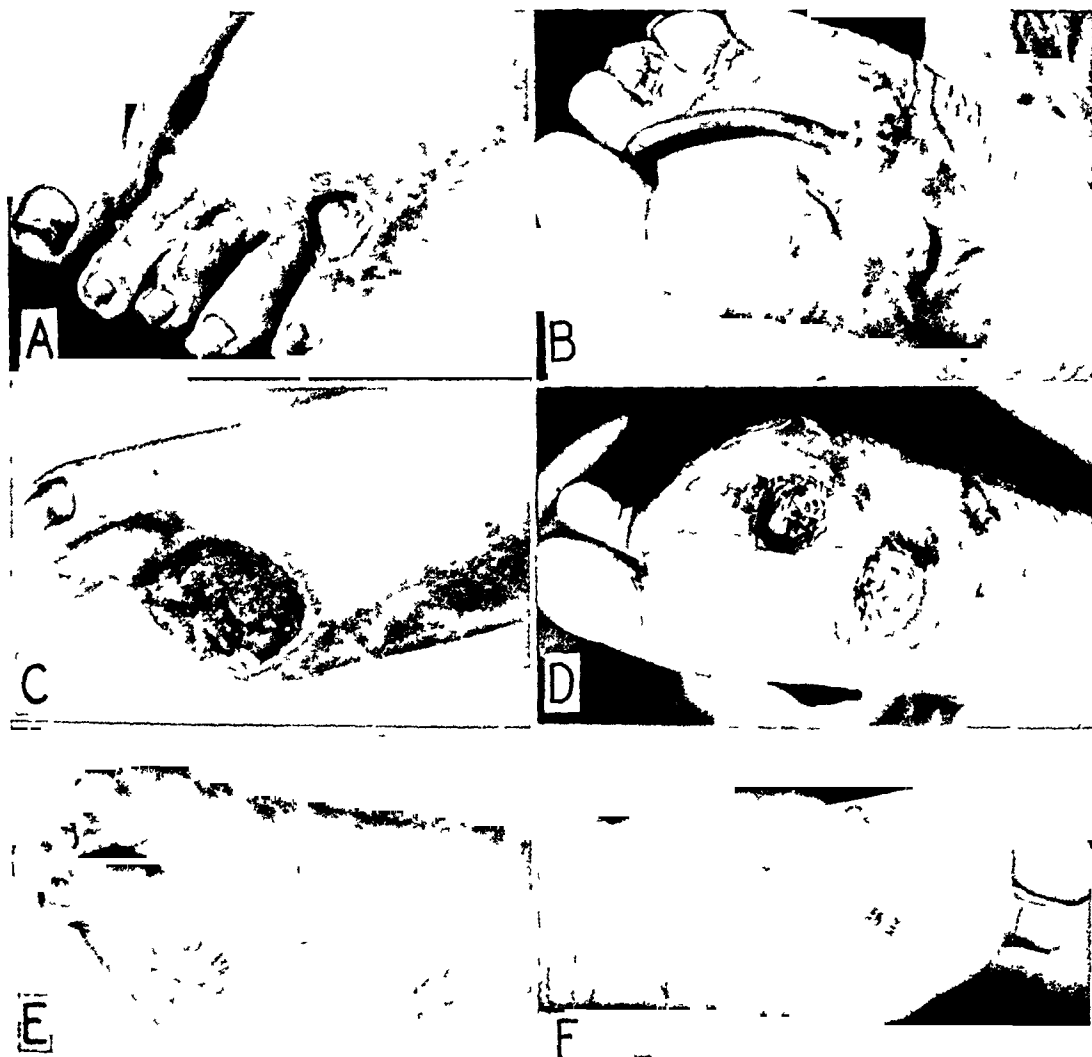


FIG 5—Case 4 Diabetic gangrene of the left third toe, with interconnected gangrenous sinuses on dorsal and plantar aspects of foot (A and B) Dorsal and plantar views before chemosurgery (C and D) Fifteen days later showing granulation tissue dorsally and adherent fixed tissue in the plantar sinuses (E and F) Six months later, showing well healed scars and good weight bearing surfaces

outlook In other words, a wet infected gangrene in a markedly inflamed foot has a better prognosis than a dry ischemic gangrene in a pale cool, unswollen foot

(5) In general, strong pulsations in the dorsalis pedis and posterior tibial arteries are good prognostic signs, but their absence does not necessarily indicate a poor prognosis, because collateral circulation may be efficient

(6) A high degree of arteriosclerosis as indicated by palpable thickening

of the radial vessels and by calcification, shown in roentgenograms of the feet, is often, but not always, indicative of a poor prognosis because a good arteriolar and capillary circulation may be present in spite of markedly sclerotic arteries



FIG 6—Case 5. Diabetic gangrene of the left great toe and dorsum of the foot with honeycombing of the entire anterior part of the foot by pus filled gangrenous sinuses. (A) Before chemosurgery. (B) Two months later showing skin closing in over granulation tissue. (C) Ten months later, showing functional stump

(7) The histamine wheal test is an excellent indicator of capillary function and, hence, of prognosis, but the same information can often be obtained by noticing the degree of inflammatory reaction to the gangrene

The rapidity with which the gangrene had progressed, the extent of the gangrene, and the amount of bone destruction were essentially without prognostic significance. In diabetics, the duration, severity and control of the diabetes were unimportant in estimating prognosis

That the efficiency of circulation in the extremity is a prime factor in determining the outcome is indicated by the finding that in 32 extremities with "fairly good" circulation, healing resulted in 93.8 per cent—there were two failures, one due to gas bacillus infection which was at ankle level when treatment was started, and one to cardiac failure in a patient who was severely

decompensated at the beginning of treatment. On the other hand in 34 extremities with a "poor" or "fair" circulation, healing occurred in ten, or 29.4 per cent. The fact that 29.4 per cent of the latter group healed, indicates that the prognostic criteria listed above are not infallible.

The Therapeutic Test—The only absolutely certain means to determine how a given case will respond, is to chemosurgically amputate the gangrenous part and observe the lesion for ten days. If by this time the layer of fixed tissue has not begun to separate it may be concluded that it will never do so and the leg should be amputated immediately.

Even if the chemosurgical amputation proves unsuccessful the patient has lost nothing as a result of the therapeutic test except the ten days. Balancing this loss of time however is the fact that the chemosurgical removal of most of the infected gangrenous tissue reduces sepsis and renders the patient a better surgical risk than he would otherwise have been.

Discussion—Why would not conservative surgical amputation be as successful as chemosurgical amputation in a similar group of cases? In the first place, the field is usually more or less infected and fresh-cut surfaces have a lower resistance to infection than the germ-resistant granulations following chemosurgery. The fixative chemical moreover, sterilizes the treated area. Second, there cannot help but be a certain amount of tissue necrosis in a surgical wound if from nothing else than the incision itself. Ligatures and sutures cause additional necrosis. These areas of dead tissue may act as a source of further extension of the gangrene. Third the optimum level for amputation cannot be selected as accurately by surgery as by the chemosurgical method which can follow out each unsuspected gangrenous sinus. Being a state institution, our hospital usually receives gangrene cases after they have become quite advanced under conservative treatment elsewhere. Therefore, few conservative surgical amputations have been feasible, however, with the chemosurgical method, a large proportion of the cases are now treated conservatively.

The saving of limbs, made possible by chemosurgery, is of special value in elderly people, usually affected by gangrene, because these patients do not readily become accustomed to artificial limbs. Moreover, the low operative risk with chemosurgery is an important advantage because the major amputations which would otherwise usually be necessary carry a mortality which may vary from 13.1 to 75 per cent in various hospitals in this country.⁴ Complicating conditions such as fever and poor control of diabetes due to infection in the extremity, do not contraindicate chemosurgery, in fact, these conditions are quickly brought under control when chemosurgical treatment is instituted.

Some degree of improvement in the results of chemosurgical amputation may well come from attempts to improve circulation during the critical period when the basal layer is separating. The use of certain proteolytic enzyme preparations during this period also shows promise of improving results in certain border-line cases.

SUMMARY AND CONCLUSIONS

The chemosurgical technic for the conservative amputation of gangrenous parts involves First, the chemical fixation of the involved tissues, and second, the surgical excision of the fixed tissues. The extraordinarily favorable healing after this procedure made possible successful results in over 60 per cent of 66 conservative amputations in a series of cases which was essentially unselected in regard to circulatory efficiency. There were no breakdowns of the scars once healing had occurred, and there were no operative deaths in this series. The method enables the conservative treatment of gangrene to be extended to a much larger group of patients than previously possible.

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DISCUSSION—DR. DAMON B. PRITTFER (Philadelphia, Pa.) Would it be possible to have a little more detailed account of the technic that is employed? I think the results are admirable.

DR. F. E. MOHS I do not know that I can make it much clearer without actually having patients to demonstrate, but the fixative is applied as a paste to the involved part. Not only the gangrenous tissue is removed, of course, but some normal tissue as well.

The zinc chloride solution is incorporated in a special base which has special properties, which I do not believe I have time to discuss now, but it is discussed in the papers that have already been published on the chemosurgical treatment of cancer (*Cancer Research*, January, 1941, *Arch Surg*, February, 1941.) It has the property of enabling penetration to be controlled over a wide range of depths by simply altering the depth of application of the paste, so that penetration can be as great as 2 cm. in 24 hours. After the tissue has been fixed to the desired depth, it is simply excised, the incision being made through the fixed tissue and not through the living tissue. If it is seen that the gangrene extends still further, the fixative is applied not only to the gangrenous area but to the whole area, so that the final wound is saucer-shaped.

A PLAN FOR THE STUDY OF WAR WOUNDS*

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THE PRESENT EMERGENCY has come upon us so soon after the last World War that many surgeons who took part then are still available for service in the Army, but most of them are over age 50 and will not be called unless they volunteer. The experience which they obtained in the treatment of war wounds gave them the knowledge of the resources available at that time, and most of them attempted to apply these principles in their civilian practice after their return. But civilian accidents simulating war wounds are relatively few and it is safe to say that, in the minds of many, the details of the methods commonly employed in those days have been forgotten, and the experience itself is fast fading from memory. But the vast number of surgeons who must be called to the colors, if we go to war, will have had no experience whatsoever in the care of war wounds, so we are faced with the problems of preparing ourselves for the work which we will have to do.

It has frequently been said that the most valuable contribution made to scientific medicine in the past war was the development of the Carrel-Dakin treatment, both in the prophylaxis and the treatment of wound infections. This was almost universally acknowledged by the surgeons of the last war and all of them, with hardly any exception, had full opportunity to demonstrate its value in the care of war wounds. It was the general consensus of opinion that its chief value consisted in its ability to liquefy necrotic tissue. However, it was not strongly bactericidal, its period of action was brief and it had to be reapplied at frequent intervals. This necessitated prolonged and frequent dressings with consequent trauma to the wound surfaces. It was also found to be mildly irritating to the tissues and an inhibitor of wound healing.

In the last 20 years, although the Carrel-Dakin treatment has been used continuously in a good many institutions, close inquiry among practicing surgeons reveals the fact that it has gradually gone out of use in most hospitals. A number of substitutes have been proposed and have been employed more or less extensively, and a number of other antiseptics quite different in their

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† Chairman of Subcommittee on Surgical Infections of the National Research Council. This paper is presented with the consent of Dr. L. H. Weed, Director of the Division of Medical Sciences of the National Research Council, Dr. Evarts Graham, Chairman of the Surgical Committee, and Dr. P. H. Long, Chairman of the Committee on Chemotherapeutic and Other Agents. The plan has been developed by and the paper written with the aid of the members of the Subcommittee on Surgical Infections—Dr. John Lockwood, Dr. Perrin Long and Dr. Champ Lyons.

chemical and physical properties have been advocated and have been used to a limited extent

Of course, civilian, accidental, contaminated wounds vary somewhat from battle casualties but the wounds of bombing victims, so numerous in the present war, are very similar to street accidents. There are, to be sure, penetrating wounds from glass and shell fragments which extensively damage deep tissues, but the great majority of these casualties are caused by falling walls, upheaving pavements, the impact of bodies thrown by the blast, and burns from various causes.

Wounds from air raids and street accidents are often crushing rather than penetrating and street dirt in this horseless age is less likely to carry tetanus bacilli than the soil of cultivated fields, but the gas gangrene organisms of human intestinal origin are ubiquitous. Compound fractures in civilian accidents are often compounded by penetration of the skin by the bone from within outward, thus minimizing bacterial contamination while bone injuries caused by missiles may be associated with gross bacterial seeding. Civilian revolver and rifle wounds are similar to rifle or machine gun bullet wounds among soldiers, but in civilian accidents there are relatively fewer wounds in which there is likely to be extensive trauma such as is produced in the deep tissues by fragments of high explosive shells.

Experience with these civilian wounds during the last 20 years has resulted in a consensus of opinion which was expressed at a Panel meeting of the American College of Surgeons in New York City in 1938. Practically all of those who voiced their point of view, at that discussion, stated emphatically that they believed these wounds should not be treated with Dakin's solution or any other form of antiseptic. All stressed the early debridement of the damaged tissue followed by immobilization of the part, with a minimum of dressing, and either a primary or a delayed primary suture. The author was the only person at that Panel discussion who advocated, in addition to the methods approved by the others, the use of an antiseptic which had recently been found which was nonirritating to the tissues, which favored wound healing, and which effectively inactivated or destroyed the organisms commonly found in contaminated wounds, namely, zinc peroxide. It was pointed out that this substance was not like ordinary antiseptics but it probably performed its bactericidal and bacteriostatic function by the gradual, slow, and continuous evolution of oxygen. It provided a highly oxygenated environment unfavorable to the growth and the toxin formation of the contaminating bacteria and it favored the proliferation of reparative tissue. Its use, however, required that the wound be left open and, because of its insolubility, it could not be used if the wound were to be closed.

At that meeting in New York, very brief mention was made of the possibility of using sulfanilamide by mouth in the prophylaxis and treatment of contaminated accidental wounds, but no one thought of the possibility or at any rate no one suggested that any of the sulfonamide drugs be applied locally to a wound as a prophylactic.

In the last two years, some very great changes have taken place in the attitude of surgeons toward the local use of antiseptics in contaminated accidental wounds, largely due to the fact that the sulfonamide drugs have come into such a prominent place in the treatment of infections. When these were first introduced, they were used principally in hemolytic streptococcus infections, first in septicemia due to puerperal fever and later in other types of hemolytic streptococcus infections of a diffuse nature.

In the early days, the scope and limitations of sulfanilamide were not well-known. It required time to develop experience with the systemic use of this drug to know how much could be tolerated by the patient and what dosage would be effective in any given condition.

The toxic effects of the drug, when given systematically, were at times alarming and the early workers in this field very properly advocated caution in expanding the scope of the new drug. It was taken up perhaps more rapidly by the medical men than by the surgeons because they had no other means to combat such widespread hemolytic streptococcus infections as pneumonia, septicemia, meningitis, and peritonitis. Moreover, it was early shown that sulfanilamide was much more effective when the infective process was diffuse than when it had become localized and was thus amenable to surgery. The effect of the drug in concentrated form on the tissues had not then been demonstrated.

It was soon found that the systemic administration of sulfanilamide would frequently abort hemolytic streptococcus infections which formerly had almost invariably progressed either to widespread cellulitis and septicemia or to abscess formation. Even when administered late in the course of a surgical infection, the drug seemed to modify favorably the course of the disease.

The earlier preparations—prontosil and sulfanilamide—showed unmistakable virtue in the control of the hemolytic streptococcus infections, but when they were applied to lesions caused by other organisms it was found that they were less effective and against some organisms they had no effect whatsoever. This led to the development of related chemical derivatives of all kinds, in the hope that the specificity of sulfanilamide might be modified so as to make it more general in its application. The failure of sulfanilamide to control non-hemolytic streptococcus, pneumococcus and staphylococcus infections was particularly disappointing, but it was soon found that sulfapyridine promptly brought pneumococcus infections to an end in most cases, and later it was discovered that sulfathiazole had an effect not only against the pneumococcus but against many strains of staphylococcus. The gas gangrene organisms and tetanus, as well as the anaerobic streptococci and gram-negative bacilli, however, continued to give very confusing and inconsistent results. The effects on certain of the gram-negative bacilli were likewise variable but some of the *B. coli* infections, particularly of the urinary tract, seemed to be favorably influenced by these drugs for they are largely eliminated through the kidneys and pass through those organs in a much higher concentration than they attain in the blood stream, without obvious damage in most cases. In some in-

stances, to be sure, the acetylated forms of the drugs, particularly sulfapyridine and sulfathiazole, mechanically block the kidney tubules but this difficulty has been largely overcome by a more adequate fluid intake

Little by little, evidence began to accumulate that these drugs might be used locally without great damage to the tissues. Concentrations a hundred times as great as could be obtained in the blood were possible if the crystalline or powder form of these drugs was placed in the soft parts. Such concentrations in the test tubes seemed not only to be more effective against the hemolytic streptococcus but had some action against certain other organisms not affected at all by the concentrations obtained in the blood stream. Furthermore, it was found that these drugs are absorbed from fresh tissue surfaces or from serous cavities and reach levels in the blood comparable to those obtained by mouth medication. After a variable length of time, the different drugs are then eliminated from the body.

Such observations made by a number of different investigators seemed to warrant the hope and expectation that these drugs might be used locally to combat established infections and to prevent the development of infections in contaminated tissue. It is natural to believe that anything which is effective in the treatment of a disease ought to be still more effective as a prophylactic.

The advent of war brought this problem very promptly to the fore and it was essential that the medical departments of the Army and Navy should attempt to evaluate the newer methods of treatment, in all kinds of medical and surgical diseases to which soldiers or civilians are particularly susceptible when they are concentrated in temporary camps, cantonments, or refuges in time of war. Likewise, it was essential that the newer methods of preventing and treating infection in accidental or intentional wounds and burns be properly evaluated and standardized. The surgeons general of the Army and Navy therefore requested professional advice from the National Research Council. The National Research Council during the past year has appointed certain committees made up of individuals particularly interested in various phases of this problem to reach a consensus of opinion or to formulate plans for studying further those questions not yet satisfactorily answered.

With many diseases common to civilian practice, it was possible for the committees to promptly agree on the best methods of treatment. With regard to the treatment of contaminated wounds, the situation was entirely different. The committee which the National Research Council appointed to consider the problem of infection in war wounds and burns was not able to draw from its own experience or obtain from any of the available literature unmistakable evidence to permit the laying down of any program or directions for the treatment of war wounds. The reluctance of the members of the surgical profession to use any form of antiseptic indicated a prejudice which had to be overcome by incontrovertible evidence that the use of the new chemotherapeutic agents, either locally or generally, (a) would do no harm, (b) would materially reduce the incidence, the severity and the duration of wound

infection as compared with simpler and safer methods, and (c) would minimize disability, disfigurement and the incidence of death

In reviewing the articles which have appeared in the medical literature not only of America but of England and the other European countries, it was apparent that most of the reports represent clinical impressions rather than demonstrated facts. In observations and reports of individual cases without proper controls, credit was given to one out of many methods of treatment used. The bacteriologic studies before, during, and after treatment were for the most part either incomplete or totally absent. Experimental work in laboratories not only failed to recognize fundamental differences between animals and man but fundamental differences between experimental and clinical conditions.

The committee, therefore, reported to the Surgeons General of the Army and Navy that it would be necessary to carry out a comprehensive and well-controlled series of clinical observations in a large number of seriously contaminated wounds among the civilian population simulating as nearly as possible contaminated wounds as seen on the battlefield or among the victims of bombing raids. In any civilian population, such cases are relatively few in number and in order to obtain a large amount of data in a relatively short time such a study would have to be carried out in a number of different centers. Furthermore, a complete and adequate study from a bacteriologic and chemical point of view could not be carried out in any given center without a staff adequately trained to cover all phases of the problem, prepared to observe the progress of the cases from start to finish in the same institution, and able to correlate and evaluate the assembled data.

A plan has, therefore, been evolved which is designed to obtain data from 2,000 cases in the course of six to nine months' time, with categories covering the various forms of treatment thought most likely to give the best results. It is believed that when the study has been completed it will be possible to lay out a program for the care and treatment of these cases which will be based on incontrovertible proof.

THE KNOWN FACTS TO DATE

Gleaned from our own experience and that of others reported in the literature in the last three years, what facts do we have to start with, which we can use as a basis for such a comprehensive plan? The following facts seem to be well established:

- (1) Accidental wounds and war wounds are all contaminated by bacteria
- (2) There is nearly always some damage to deep tissues with extravasation of blood. Sometimes there is tearing of muscle and fracture of bone
- (3) The growth of organisms is favored by the presence of injured tissue and foreign bodies introduced into such wounds
- (4) Certain organisms get into the wound at the time of the accident and others contaminate it later as long as it remains open

(5) Any organism which gets into a wound may find conditions favorable to its growth enabling it to colonize in the wound and produce its poisons. This may take place as early as two to three hours after contamination.

(6) Motion in any infected tissue increases the activity of the infection.

(7) Surgical debridement will remove a large proportion of the contaminating organisms, foreign bodies, and damaged tissue.

(8) Such wounds cannot be completely sterilized by any known procedure, but the proportion of organisms removed by debridement depends upon the care that is employed and the time after contamination that the operation takes place.

(9) Some debrided wounds may be closed with impunity and may heal without infection, while others so treated may become infected depending upon the completeness of the debridement, the time of the debridement after injury, and the number and virulence of the organisms still present after the debridement has been completed.

(10) Leaving debrided wounds open decreases the probability of serious infection but permits secondary contamination of the wound if proper precautions are not taken. Contaminating organisms may grow on the surface of a wound and not necessarily delay its healing. Hemolytic streptococci coming from nose or throat of attendants not infrequently secondarily infect open wounds.

(11) Patients who have received accidental injuries are frequently in shock when they reach a hospital.

(12) Sulfanilamide may be taken by mouth in doses of six grams initially and six grams in 24 hours distributed at four-hour intervals without serious consequences in most cases and this will maintain a level in the blood of approximately 5-10 mg per cent as long as it is being given.

(13) Sulfapyridine may be so administered, but it is very nauseating and much more difficult to maintain a constant blood level because of its variable and generally slower rate of absorption.

(14) Sulfathiazole may be so administered and is less nauseating than sulfapyridine but is even more difficult to maintain a constant blood level.

(15) Sulfanilamide when given by mouth is particularly effective against the hemolytic streptococcus and will prevent its growth and spread from almost any portal of entry. It is relatively less effective against other organisms.

(16) Sulfapyridine when given by mouth is effective against the hemolytic streptococcus and pneumococcus, but it has relatively less effect on the other organisms.

(17) Sulfathiazole when given by mouth is effective against the pneumococcus, and to some extent the *Staphylococcus aureus*, the hemolytic streptococcus and *B coli*, but it has relatively less effect on other organisms.

(18) The effect of these drugs when given by mouth has a variable and uncertain effect on the gas gangrene and tetanus clostridia and the anaer-

obic gram-negative bacilli and streptococci

(19) The bactericidal and bacteriostatic effects of these drugs are handicapped or inhibited by the presence of pus or exudate, or split products of protein, especially peptones, which are present in pus or damaged tissue

(20) Sulfanilamide, sulfapyridine, and sulfathiazole may produce mild, moderate, or profound intoxication and injury to the red cells, the white cells, and the bone marrow. They may produce skin rashes, fever, jaundice or delirium and the acetylated forms of the latter two may block the kidney tubules and thus produce anuria. In a few cases of idiosyncrasy, these effects may take place promptly after the drug's administration, but usually they do not occur until the second week of administration

(21) The toxic effects of the drugs generally stop promptly after withdrawal of the drugs

(22) These drugs may be applied in crystalline or powder form to fresh wound surfaces without serious damage to those tissues. They go into solution in the tissue fluids in concentrations ranging from 200 to 1,000 mg per cent

(23) Sulfanilamide is absorbed quickly from such wound surfaces, reaches a peak level in the blood stream in 8 to 12 hours and is eliminated completely in four-five days

(24) Sulfapyridine and sulfathiazole, absorbed much more slowly, reach a lower and variable level in the blood stream but they both persist longer than sulfanilamide in the blood stream

(25) A creamy suspension of medicinal grade zinc peroxide powder in distilled water when instilled into a debrided wound, if kept wet, will not injure tissue or have any untoward systemic effect or damage blood cells or any other organs or tissues. To be effective it must come in contact with every part of the wound surface

(26) Zinc peroxide will kill many of the contaminating organisms and prevent the growth and activity of others. It is particularly effective against all of the anaerobic organisms, the hemolytic streptococcus, and the pneumococcus

FURTHER IMPORTANT DATA

(1) Evidence has been presented tending to the belief that mild roentgenotherapy will readily penetrate injured tissue and may produce conditions unfavorable to the development and growth of bacteria

(2) There are numerous reports of clinical experiences with the sulfonamide drugs, with zinc peroxide and with roentgenotherapy which claim but do not clearly prove the value of these agents in the prevention and treatment of infection in contaminated wounds

(3) There are other substances such as gramicidin, penicillin, and chlorophyl which may have little or no damaging effect on local tissues and may inhibit the growth of certain of the contaminating organisms. These may merit a clinical trial

(4) Incontrovertible evidence is not yet available to indicate which agent is best or how it may best be employed

On the basis of this knowledge and these beliefs, we can set up a rational plan for the study of badly contaminated civilian accidental wounds of soft parts and compound fractures and burns or war wounds in the following manner

THE PLAN

(1) A unit of ten hospital beds should be set up in each of ten of the larger cities of the country in an hospital equipped with every facility for the proper care of seriously injured patients. Arrangements should be made with the city Department of Health or hospitals to promptly transfer such patients by ambulance directly from the scene of the accident to the hospital

(2) There should be a director to oversee the work of the unit who shall be responsible for the proper care of the patients, see that the proper laboratory tests are carried out, observe and record the clinical progress of the cases from day to day, and collect and summarize all of the data when the case is closed

(3) There must be a group of surgeons available who are competent to perform all of the surgical procedures necessary in the care of such cases and willing to conform to certain standard procedures agreed upon at the outset of the study

(4) There must be a bacteriology laboratory fully equipped with personnel and apparatus to make complete bacteriologic analyses and classification of the bacterial flora of all of the contaminated wounds by certain specified aerobic and anaerobic procedures

(5) There must be a chemical laboratory fully equipped to make chemical studies of blood levels of drug concentration, red and white blood cell counts, and urinalyses. An expert radiologist must help

(6) When the case is closed, all of the data connected with each case must be recorded on a summary sheet which lists everything that will indicate the effect of the treatment administered and the results obtained. The summary sheet will be so designed that the data may be promptly transferable to punch cards for statistical purposes. One such sheet shall be kept with the hospital chart and a duplicate sent to a central office for carding and filing

(7) Upon the admission of the patient to the hospital, the director shall coordinate the care and the study of the case. In conference with the operating surgeon, he shall decide whether to have the patient operated upon at once or given certain ante-operative preparations, for example shock treatment. The wound shall be covered with a sterile dressing until the time of operation

(8) As soon as the patient is in proper condition for operation, he shall be taken to the operating room and anesthetized. The area of the wound or burn shall be cleansed in a specified manner. The wound shall be thoroughly debrided in a standard way

STUDY OF WAR WOUNDS

(9) All of the débrided tissue shall be placed in a sterile container and taken to the bacteriology laboratory within half an hour to be cultured in a specified manner

(10) The débrided wound shall be washed thoroughly and a culture made from the last wash water, presumably revealing what organisms were still in the wound at the end of the procedure

(11) If the operation occurs within six hours of the time of the accident, the operator may decide whether or not to close it by suture with or without draining. If it occurs more than six hours after the accident, it must be left open

(12) Thus there shall be a series of cases of closed wounds and a comparable series of open wounds. In each series, by means of a card system or its equivalent, the cases in each group shall alternate receiving or not receiving some sulfonamide compound by mouth and each of these subgroups shall rotate on local treatment as follows

Closed wound without sulfonamide compound by mouth

- (a) Nothing locally
- (b) Sulfonamide compound locally
- (c) Roentgenotherapy

Closed wound with sulfonamide compound by mouth

- (a) Nothing locally
- (b) Sulfonamide compound locally

Open wound without sulfonamide compound by mouth

- (a) Nothing locally
- (b) Sulfonamide compound locally
- (c) Roentgenotherapy
- (d) Zinc peroxide locally

Open wound with sulfonamide compound by mouth

- (a) Nothing locally
- (b) Sulfonamide compound locally
- (c) Zinc peroxide locally

(13) Burned patients will be anesthetized and the burned area will be thoroughly cleansed. All of the skin blisters will be taken to the laboratory for culture. The cases will then be divided into two main categories, one with and one without some sulfonamide compound systemically. In each of these groups, there will be two methods of local treatment. The first will be the application of 5 per cent tannic acid and silver nitrate solutions to all burned surfaces. The other group will have the same treatment for body burns but frequent changes of wet dressings of 1 per cent sodium chloride and 0.25 per cent sodium citrate over gauze impregnated with tulle gras for face and hand burns

This study, therefore, calls for 12 treatment categories for wounds and four for burns. These categories shall be currently compared with one another by means of the punch cards and shall be correlated with the bacterial analyses so that the best form of treatment for any given type of wound and any given type of bacterial contamination will gradually evolve. If any form of treatment is obviously giving unsatisfactory results, after the study has been going on for a number of months, that category may be dropped and if indicated another added in its place.

The study of the prevention of infection in any given case need not be carried over a period of ten days. By that time, we will know whether or not the treatment has been effective in preventing infection. The case may then be turned over to the general surgical service for further care or convalescence.

It is estimated that data may thus be obtained on 2,000 cases with sufficient numbers in each category to permit an evaluation of these various methods of treatment and this method may then be applied to real war wounds.

It is obvious that such a comprehensive study will cost a considerable amount of money—the largest item of expense will be the hospitalization costs for the patients. The whole study calls for a budget of about a third of a million dollars. But when one considers that this represents the amount of Army life insurance on only 35 soldiers, there can be no question of the appropriateness and value of the investment. The right answer to this question of the best treatment for the prevention of infection in war wounds will save the lives of thousands, lessen the complete or partial, temporary, or permanent disability of many more thousands, shorten the hospital stay, and lessen the hospital costs of all wounded soldiers and civilians, and prove of benefit to mankind for all time.

Such a study cannot be carried out properly under the stress of war. It can only be undertaken in a nonbelligerent country. I believe that it can best be done here in the United States. The time is fast approaching when we may be actively engaged in the war. It may be impossible for us to carry out this essential study if we delay any longer in initiating the project. Further delay or curtailment of appropriations for this study might make it necessary to compromise on this plan by cutting out certain categories, but this would materially lessen its value and it is hoped that this can be avoided.

PROCAINE INJECTION AND EARLY MOBILIZATION IN THE TREATMENT OF NON-WEIGHT-BEARING FRACTURES*

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IN THE modern treatment of fractures, it is now fairly well recognized that the maintenance of active function during the period of fracture healing reduces the period of disability and, by thus maintaining a normal blood supply, hastens union.

A favorable experience in the application of this principle has led us to examine the possibilities of the method of Leriche. He suggested that non-weight-bearing fractures could be treated by the injection of procaine solution and by early mobilization. His first article¹ appeared in 1928 and, since then, some 30 or more articles, mostly by Leriche and his students, have appeared in the French literature, with scattered articles in the Argentine, Brazilian and English, and one in the American literature. More than 200 fractures have been reported as successfully treated by this method. We wish to discuss, briefly, the theory underlying this method of fracture therapy and to cite the results we have obtained in 84 cases thus treated.

It goes without saying that this form of treatment is contrary to the long-established principles of rest and immobilization as the best method of promoting healing in injured parts. In fact, the accepted medical thought on this subject is probably exemplified by the following question and answer, which appeared in the Journal of the American Medical Association for August 13, 1938²:

Question "Is it considered good practice to inject procaine hydrochloride into a sprained knee as routine treatment? An osteopath nearby is doing this in order that children may continue to play basketball. I advised taping the sprained knee, with rest." M. D., Colorado

Answer "A sprain of any kind indicates injury to supporting tissues. A sprained knee should be protected against reinjury and supported either by a splint or by adhesive strapping and an elastic bandage until the injured tissues have had time to repair. Injection of procaine hydrochloride into a sprained joint, to relieve the pain so that activity may be made possible, is a dangerous procedure. The pain which is present, after such an injury, is nature's way of warning the individual that damage has been done and that further activity producing the pain is increasing the injury. The local anesthetic simply paralyzes the warning signal and is as much a mistake as it would be to disconnect the burglar or fire alarm simply because the sound of it annoyed the owner of the establishment in which it had been installed."

* Read before the American Surgical Association, White Sulphur Springs, W. Va., April 28, 29, 30, 1941.

The theory underlying the beneficial effects obtained by procaine injection is extremely interesting. The value of the procaine in the treatment of fractures lies not in the abolition of pain, but in eliminating the vasomotor impulses due to trauma. Albert³ showed the presence of these reflexes in experimental work, in 1924. He found them most pronounced following articular and para-articular trauma, and noted that the amount of vasospasm seems to bear no definite relation to the anatomic extent of the lesion. He believes this to be an axon reflex, as section of all the anterior and posterior spinal roots does not abolish this vasomotor reaction to trauma. Ochsner and DeBailey⁴ have added further to our knowledge of this mechanism in their work on thrombophlebitis. Experimentally, they showed that localized chemical endophlebitis results in marked arteriolar vasospasm of such severe degree that practically all pulsations are lost. They believe that this mechanism is the result of vasoconstrictor impulses originating in the involved segment and transmitted over the sympathetic nervous system, because it can be prevented by performing a sympathectomy or by blocking the sympathetic ganglia with procaine hydrochloride. They have explained the physiologic basis for the edema associated with vasospasm.

Leriche believed that the pain and disability produced by fractures near joints was the result of the same type of reflex. He obtained relief of pain and a resumption of almost normal function by interrupting the reflex arc by the injection of the sympathetic ganglia supplying the part or by local infiltration of the fracture site. We have noted also a reduction of edema following the injection of procaine solution at the injured area. That the abolition of pain *per se* is not the value of this form of therapy is further borne out by Leriche's⁵ observation that, when adrenalin is added to the procaine solution (vasoconstriction), the desired effect is not obtained, though the anesthetic effect of the procaine is prolonged. Furthermore, the pain relief persists for eight to ten hours after the anesthetic effect of procaine should have disappeared.

Leriche is so enthusiastic about the value of procaine that he recommends it to be used whether the fracture is mobilized or not. Outland and Hanlon⁶ have observed that fractures reduced under local anesthesia and then immobilized in plaster are more pain-free and are accompanied by an earlier resumption of function than when general anesthesia is used. In this connection, it is interesting to cite our experience with a Colles' fracture reduced under local anesthesia and placed in a plaster encasement. The following day the patient was quite comfortable except for pain over the ulnar styloid, which had not been infiltrated the previous day. This pain was relieved by an injection of the cervical sympathetic, and did not recur.

The question naturally arises as to whether or not active function by early mobilization is of more beneficial effect than the procaine injection. In five fractures, excellent results were obtained by early mobilization without procaine infiltration. Three of these were in infants, and in all cases there was no edema or marked pain.

We believe the procaine injection relieves the discomfort and edema, thus permitting early resumption of active function. These two measures allow a more adequate blood supply to be maintained, which produces an early and excellent fracture healing.

Early mobilization is of special value in minor fractures in the region of joints. With maintenance of active function during the period of fracture healing, nature is able to accommodate for the deformities in the articulating surfaces as they occur in the actual use of the joint. When these fractures are treated by immobilization during the period of fracture healing, the accommodation is only for the position in which the fracture is immobilized. This is best exemplified in fractures of the head or neck of the radius. The limitation of motion resulting in these fractures treated by immobilization is well known, whereas treatment by mobilization preserves almost normal function, even with some displacements of the fragments. Fontaine⁷ was the first to point out this fact, and our experience has borne out his contention.

Summarizing the theoretic background, a fairly logical sequence of events is that the original trauma produces a reflex vasospasm which causes local anoxia. This increases the permeability of the capillary walls and results in edema, which causes further pain and so *ad infinitum*. Local injection of procaine interrupts the reflex arc, in this way relieving reflex vasospasm, thus reversing the cycle. Thorndike's⁸ good results in the use of pressure dressings may well be due to an attack on this cycle at another point, that is, the edema. Improvement in the blood supply and prevention of edema are the desired effects, whether they are obtained by active motion, by blocking the vasoconstrictor impulses with local injections or ganglion infiltration with procaine or by preventing edema by applying a pressure dressing. Active function permits rapid fracture healing and an accommodation for minor articular deformities so that almost normal joint function can be preserved.

Method—With aseptic precautions, after thorough sterilization of the skin, 1 or 2 per cent procaine hydrochloride solution, without adrenalin, is injected at the point of maximum tenderness. The amount varies, the injection being continued until complete relief of pain is obtained. The involved member is massaged to insure thorough dissemination of the solution and, at the same time, probably aiding the absorption of the local edema. We have used elastic or elastic-adhesive bandages, especially in fractures around the ankle joint, though Leriche apparently uses no supportive dressing. The patient is then instructed to use the part normally but not to put it to a test.

These patients occasionally have systemic effects as manifested by a feeling of faintness and marked perspiration. Many have an increase in pain eight to 12 hours after injection but this gradually subsides. It is well to warn the patient about this. The injections are repeated as deemed necessary, though we have not given them as frequently as Leriche.

Injection and immediate mobilization is not always used as a primary treatment. In fractures with marked swelling due to hemorrhage, we have

applied compression bandages or splints with elevation of the part until the swelling begins to recede. This means three to five days, after which we inject and begin mobilization.

Indications and Contraindications—Not every fracture lends itself to injection and mobilization. It cannot be used in fractures of weight-bearing bones nor in those which require immobilization dressings for maintaining reduction. It may be used, however, in fractures of non-weight-bearing bones which do not require reduction and is especially indicated in fractures about joints.

Advantages—The advantages of this method of therapy lie not alone in its relief of pain. One of its chief virtues consists in the ability to permit the patient to resume normal or slightly restricted function at an early date, without the disability of cumbersome splints or plaster encasements and crutches or canes. The final and important advantage is the excellent functional results which can be obtained, avoiding in some instances prolonged and even permanent disability that is often encountered in articular fractures treated by immobilization.

Results—We have treated 84 fractures by early mobilization, with procaine injections in all but four cases (Table I). All but four cases had satisfactory results. The various types of fractures and the results obtained are discussed in their anatomic groups.

TABLE I
SUMMARY OF FRACTURES TREATED BY PROCAINE INJECTION AND MOBILIZATION

Clavicle	4	Shaft of fibula	1
Upper end of humerus	6*	Around the ankle	22*
Around the elbow	9	Tarsometatarsals	13
Both bones of forearm	1	Phalanges of toes	6*
Radial styloid	5	Ribs	5
Metacarpals	7	Transverse processes of lumbar vertebrae	2
Phalanges of fingers	3*		

Total

84

* One of these fractures not injected

Fractures about the Ankle—The greater number of reported fractures treated by this method have been around the ankle joint. These vary in degree from sprain fractures of one malleolus to trimalleolar fractures without displacement. Campbell⁹ believes only minor fractures around the ankle joint should be treated in this manner. He defines a minor fracture as one in which only one malleolus is broken with an intact ligament on the opposite side, as evidenced by the absence of pain on pushing the foot toward the fractured side. Cullumbine¹⁰ increases the indication to those in which there is no displacement. We treated 22 fractures around the ankle joint, of these, there were six sprain-fractures, one internal malleolus, 11 external malleoli, two bimalleolar and two bimalleolar with posterior lipping fractures (Table II).

These cases were all allowed to bear weight on an average of four days after fracture, the quickest weight-bearing being immediate, and the longest 14 days after injury. The average period of disability was 15 days, the

NON-WEIGHT-BEARING FRACTURES

extremes being three and 30 days. This does not mean these patients' ankles were perfectly normal, but they were able to go about their usual occupation without much discomfort. In addition to an average of two injections,

TABLE II
FRACTURES AROUND THE ANKLE

Case	Age	Fracture	Other Treatment	Injec- tions	Weight- Bearing Day	Days Dis- ability	Result
E S	35	Sprain ext mal	Elastic adhesive bandage	2	1	5	Good
R W	12	Sprain ext mal	Splint 6 days	1	7	14	Good
C P	29	Sprain ext mal	Strapping	1	1	8	Good
B O		Sprain ext mal	Strapping	1	1	3	Excellent
W C	15	Sprain ext mal	Gelatin boot	1	1	13	Excellent
W F	22	Sprain tibia	Elastic adhesive bandage	2	1		Good
E D	21	Ext mal	Elastic adhesive bandage	1	1	7	Excellent
E F	15	Ext mal	Elastic adhesive bandage	2	7	14	Good
J M	26	Ext mal	Plaster splint, 2 days	0	3	3	Excellent
S R	41	Ext mal	Strapping	1	1	10	Excellent
C W	32	Ext mal	Gelatin boot	2	2	6	Excellent
W B	47	Ext mal	Strapping	2	12	30	Fair
W M	20	Ext mal	Splint 5 days, strapping	2	5	19	Excellent
L L	41	Ext mal	Gelatin boot	1	1	13	Excellent
M B	71	Ext mal	Gelatin boot	2	1	22	Good
G B	52	Ext mal	Gibney boot	2	1	20	Good
C W	20	Ext mal	Ace bandage	2	14	30	Excellent
F S	56	Int mal	Strapping	1	2	14	Excellent
P H	42	Ext mal and posterior lip	None	3	3	12	Good
A P	44	Ext mal and int mal	Strapping	1	1	30	Fair
E B	18	Trimal	Splint 6 days	1	6	13	Excellent
L W	22	Trimal	Splint 6 days, Ace bandage	3	6	13	Excellent

practically all these patients had some form of pressure dressing, either elastic adhesive, Gibney boot or gelatin boot. Results were evaluated as follows: 12 excellent, eight good, two fair, none was unsatisfactory. These results were based on the amount of pain the patient experienced, the period of disability, the eventual end-result, and the patient's satisfaction with the treatment.

In these fractures about the ankle, sprain-fractures, fissure-fractures (Fig 1) and fractures of the fibula above the malleolus (Fig 2), respond very well to this form of therapy. Greater care, perhaps with temporary (five or six days) splinting, must be exercised in bimalleolar and trimalleolar fractures, in order to insure preservation of the mortise (Fig 3).

Tarsal and Metatarsal Fractures—There were 13 patients in this group (Table III). The average period of disability was about ten days, the shortest one being one day and the longest 30 days. Six patients were able to resume normal function in five days or less. Four others were not seen for treatment until six to ten days after the fracture.

The commonest site of injury was the base of the fifth metatarsal. In addition to the procaine injections, adhesive strapping or other support was usually employed and the patient was asked to walk immediately. Practically all patients walked without the aid of crutches following the first injection. An excellent result showing the saving in time and compensation was obtained in one patient (Fig 4).

Fractures of Phalanges—In this group are nine cases—six of the toes

and three of the fingers (Table IV) The fractures of the toes were mostly complete fractures of the proximal phalanges

Fractures of the toes are very difficult to immobilize properly The average tongue-depressor splint places an additional strain on the fracture site and frequently increases the discomfort We have found that injection

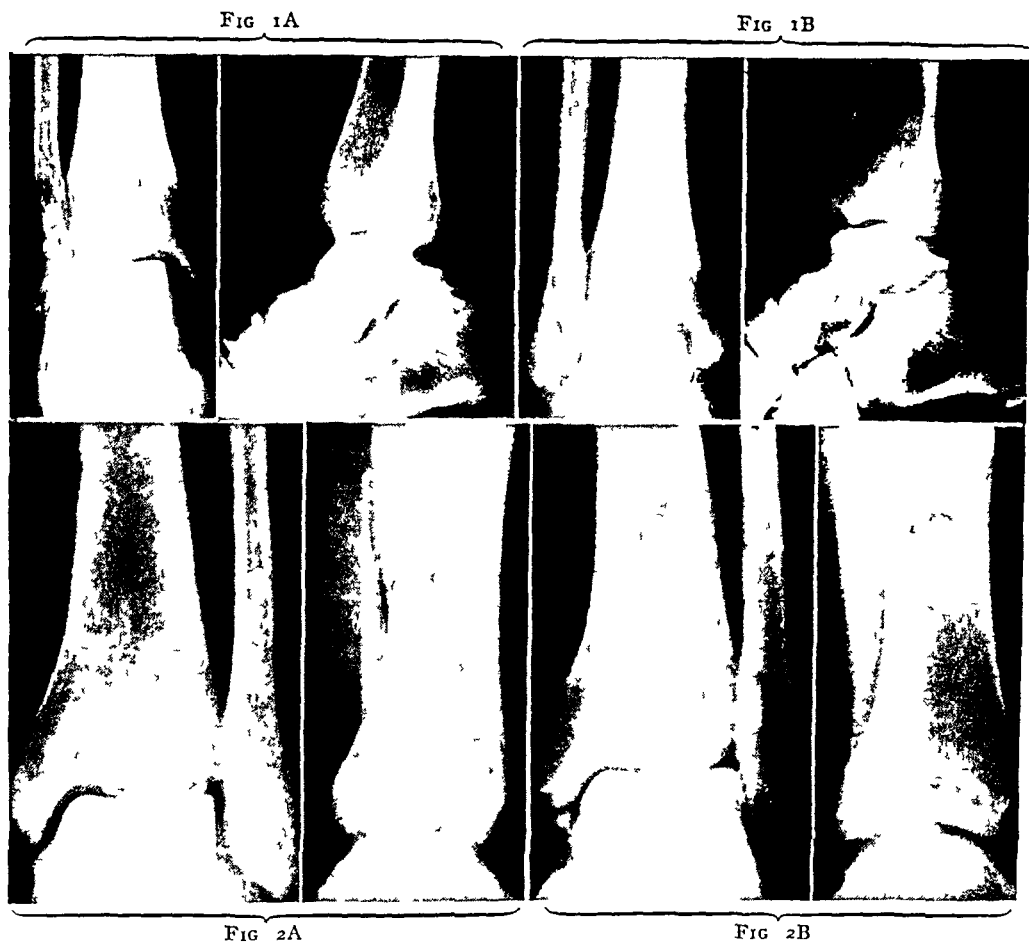


FIG 1—(A) Fracture of lower fibula January 19, 1940. One injection of procaine, elastic adhesive bandage crutches for one week, seventeenth day no pain or disability. Lost three days work. (B) Follow up roentgenograms, March 13, 1941.

FIG 2—(A) Fracture of lower fibula March 13, 1940. Plaster splint, six days, one procaine injection, elastic adhesive bandage. Walked with no disability in 14 days. (B) Follow up roentgenograms, April 19, 1941.

and support with snug adhesive strapping results in rapid union in these fractures, with a minimum of disability and inconvenience (Fig 5)

Small chip-fractures of the phalanges of fingers are best treated by mobilization. Probably, everyone has seen stiff fingers resulting from immobilization due to adhesions of the extensor tendon. These are extremely difficult cases to treat and we believe they can be prevented by procaine injection and early mobilization.

Fractures of the Upper End of the Humerus—Six fractures of the upper humerus were treated by injection and early mobilization (Table V). All had impaction with displacement of minor degree. The greater tuberosity was fractured in three cases. In all but one case, some form of fracture

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TABLE III
FRACTURES OF TARSO METATARSALS

Case	Age	Fracture	Other Treatment	Injections	Days Disability*	Result
R O	32	Prox end 5th metatarsal	Adhesive strapping	2	30†	Fair
R G	17	Prox end 5th metatarsal	Adhesive strapping	2	5	Good
A Z	16	Prox end 5th metatarsal	Adhesive strapping	3	11	Good
F F	13	Prox end 5th metatarsal	Adhesive strapping	1	4	Excellent
L C	21	Prox end 5th metatarsal	None	1	5	Excellent
M F	17	Prox end 5th metatarsal	Strapped 6 days	2	12	Excellent
J F	60	4th 5th metatarsals	Strapped and rest 7 days	1	16	Excellent
M M	31	3rd metatarsal	Strapping	1	10	Good
C L	47	2nd metatarsal	Strapping	2	1	Excellent
P D	45	1st metatarsal	Gelatin boot	1	5	Good
J D	20	1st cuneiform	Encasement 7 days	1	10	Excellent
N H	20	Sprain tarsometatarsal joint	None	2	9	Excellent
F F	13	Os vesalianum	None	2	5	Excellent

* Average period of disability 10 days

† Patient did not cooperate, would not try to use foot

TABLE IV
FRACTURES OF THE PHALANXES

TOES

Case	Age	Fracture	Other Treatment	Injections	Days Disability*	Result
D S	28	Proximal phalanx 1st toe	None	0	2	Excellent
R L	22	Distal phalanx 1st toe	Strapping	1	14	Excellent
E C	35	Proximal phalanx 5th toe	Splinted 8 days before elsewhere	1	31	Excellent
M L	24	Proximal phalanx 1st toe	Strapped	2	1	Excellent
W J	18	Proximal phalanx 2nd toe	Strapping	1	3	Good
J B	40	Proximal phalanx 5th toe	Splint 5 days	2	6	Excellent

* Average period of disability 9 days

FINGERS

Case	Age	Fracture	Other Treatment	Injections	Days Disability*	Result
M L	37	Middle phalanx 4th fing	Hairpin splint	1	16	Good
M P	37	Distal phalanx 4th fing	Splint 13 days	1	14	Good
J M	25	Chip fracture middle phalanx 2nd finger	Splint 2 days	3	7	Excellent

* Average period of disability 12 days

TABLE V
FRACTURES OF THE UPPER END OF THE HUMERUS

Case	Age	Fracture	Other Treatment	Injections	Days, Disability*	Result
J B	55	Surg neck and greater tuberosity	Axillary pad 3 days, sling	3	21	Excellent
L G	59	Surg neck and greater tuberosity	Hanging case 4 weeks	3	35	Excellent
E H	60	Greater tuberosity	None	2	21	Excellent
M F	48	Surgical neck	Hanging case 4 weeks	1	42	Fair
F M	71	Surgical neck	Body swathe	1		Unsatisfactory†
E W	65	Surgical neck	Body swathe	1	42	Fair

* Average period of disability 32 days

† Follow-up 5 months later Patient able to put hand on the top of head

dressings was used for a time, but was discarded as soon as the patient would use the arm. The best results were obtained in private patients, who would cooperate by making an effort to resume active function. All cases had good end-results. Three, with fractures of the greater tuberosity, had almost 100

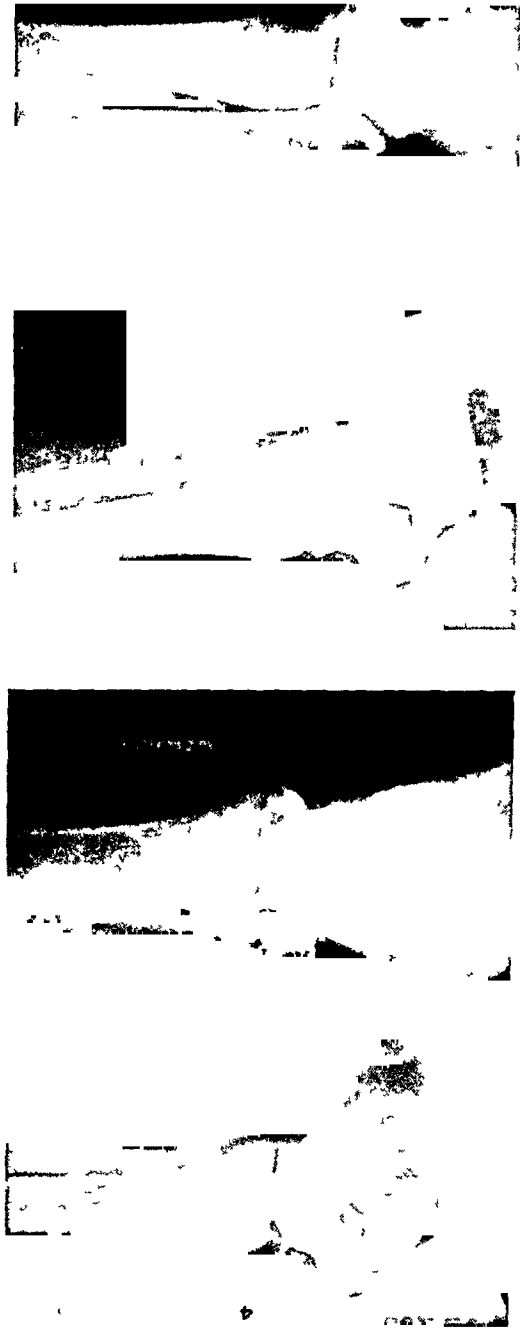


Fig 3—(A) Bimalleolar and posterior marginal fracture. Plaster splint for six days, three procaine injections, elastic adhesive bandage. Went on trip and was walking well, thirteenth day, played nine holes of golf and danced the third week. (B) "Can hardly tell which ankle was broken," February 17, 1941

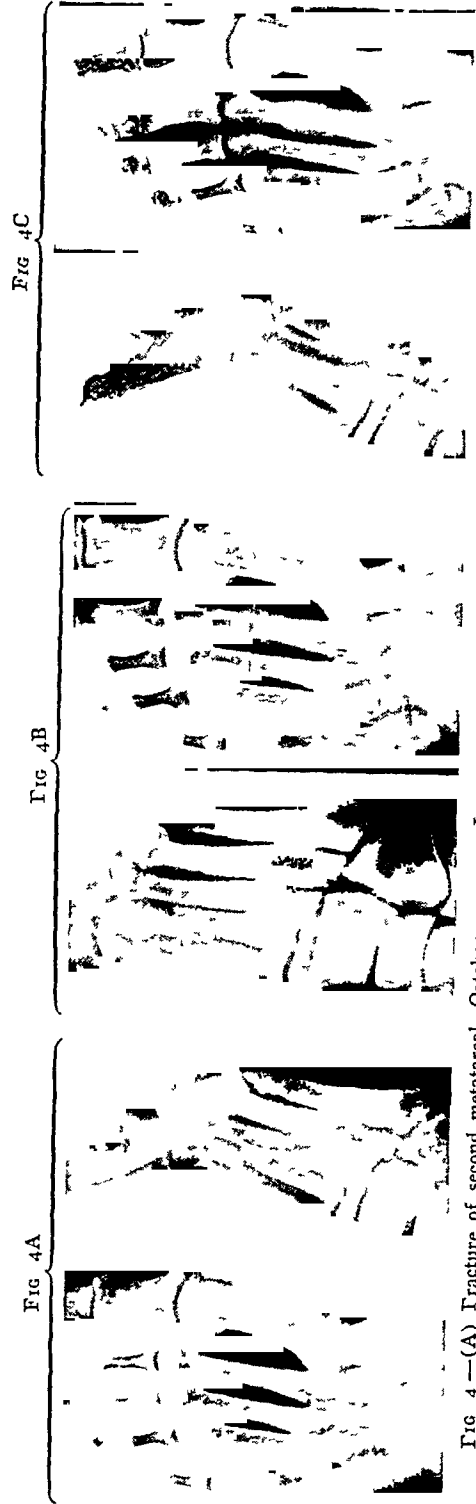


Fig 4A

Fig 4B

Fig 4C

Fig 4—(A) Fracture of second metatarsal, October 3, 1940. Injected with procaine and foot strapped, patient bowled the same evening wore his usual shoes, and lost no time from work. One reinjection and two restrappings. (B) Rapid calcification of callus, October 30, 1940. (C) Follow up, January 28, 1941

per cent shoulder function within two and one-half months after injury. In our experience, this is quite unusual for this type of fracture in the older age-group (Fig 6)

Fractures around the Elbow—There were nine patients with fractures in the region of the elbow, two of these were bilateral, making 11 fractures (Table VI). The limitation of motion which follows the immobilization of these fractures does not appear when active function is permitted during the early stages of fracture healing. The average period of disability of the elbow was ten days in these 11 fractures. Exceptional results were noted in four fractures of the head and neck of the radius. All cases obtained almost normal functional results in eight to 12 days.

We have had no instance of an ossifying hematoma appearing in the small series treated by this method (Fig 7)

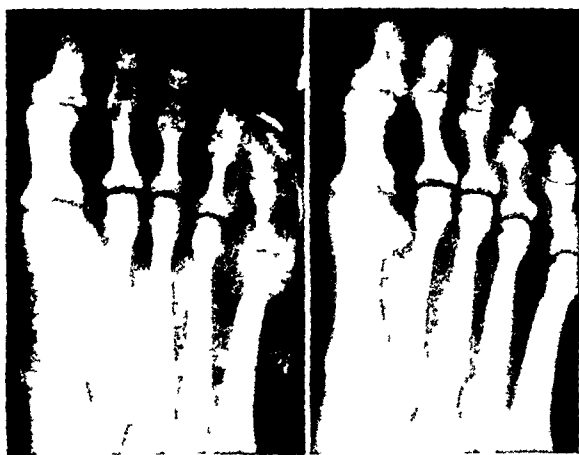


FIG 5A and B

FIG 5—Treated by splint elsewhere, had continued pain. (A) Roentgenogram, September 4, 1940, one month after fracture shows no union. Splint removed, injected with procaine, toe strapped. Played in tennis tournament three days later. (B) Follow up roentgenogram, April 8, 1941.

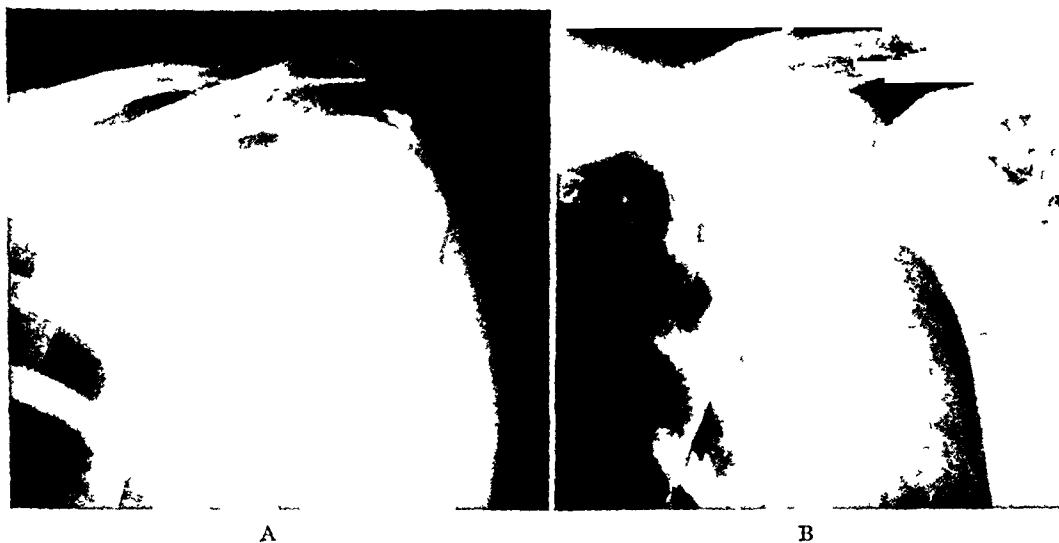


FIG 6—(A) Fracture of greater tuberosity, January 31, 1941. Three procaine injections and active mobilization of arm and shoulder. (B) Full normal function, April 12, 1941.

TABLE VI
FRACTURES ABOUT THE ELBOW

Case	Age	Fracture	Other Treatment	Injections	Days	Disability*	Result
H Y	41	Int epicondyle humerus	None	2		11	Good
H M	21	Ext epicondyle humerus	Sling	4		9	Excellent
P A	20	Int epicondyle humerus	Sling	1		16	Good
D C	3	Condyles both humeri	None	0		10	Excellent
R E	48	Malunion—old callus	Splint 2 days Sling 2 weeks	2		14	Excellent
A B	40	Neck of radius	Splint 10 days	2		12	Excellent
J K	9	Neck of both radii	None	1		9	Excellent
J R	28	Head of radius	None	1		8	Excellent
D F	23	Olecranon	Splint 2 days	1		2	Good, incomplete follow up

* Average period of disability 10 days



FIG 7—Pain and slight swelling over head of radius, inability to flex or extend elbow or rotate forearm. Procaine injection, 20 cc of 1 per cent solution, no immobilization. No spontaneous pain the following day, ten days later, almost complete function of elbow, driving his car.

Fractures of the Lower End of the Radius—The five fractures of the lower end of the radius were all so-called check- or crumble-fractures, with fracture of the styloid process (Table VII). However, there was consider-

TABLE VII
FRACTURES OF THE LOWER END OF THE RADIUS

Case	Age	Fracture	Other Treatment	Injections	Days	Disability*	Result
M S	49	Styloid of left radius	Splint 6 days	1		11	Good
D C	45	Radial styloid	Splint 2 days	1		7	Excellent
M W	69	Radial styloid	Splint 1 day	1		10	Excellent
G H	58	Radial styloid	Splint 9 days	2		14	Excellent
M F	—	Radial styloid	Splint 6 days	1		8	Excellent

* Average period of disability 10 days

able edema, pain, and disability present, although there was no displacement. In other words, these were cases which would probably have been diagnosed as a bad sprain before the days of roentgenography.

One patient, age 45, with a check-fracture of the radius and a chip-fracture of the cuneiform, was injected with procaine after four days' immobilization on a hand-splint. On removal of the splint, any voluntary motion of the fingers was painful. She was unable to pick up her pocket-book. Immediately after injection, she was able to pick up objects. Three days later she was able to use her hand. She had not experienced the usual after-pain. Six days after injection, all swelling had disappeared, the patient had no pain, but there was still slight tenderness over the radial styloid. One month later, function was excellent, and there was no pain present.

TABLE VIII
FRACTURES OF THE METACARPALS

Case	Age	Fracture	Other Treatment	Injections	Days	Disability*	Result
F D	18	1st metacarpal	Encasement	1	21		Unsatisfactory
T D	39	2nd metacarpal	None	2	4		Excellent
P T	48	5th metacarpal	Encasement	1	28		Unsatisfactory
E H	33	5th metacarpal	Splint 8 days	1	10		Excellent
G S	19	5th metacarpal	Splint 4 days	1	14		Good
J P	21	5th metacarpal	Splint 3 days	1			Incomplete follow up
A F	23	5th metacarpal	None	1	25		Excellent

* Average period of disability 17 days

Metacarpal Fractures—Metacarpal fractures vied with those of the ribs in giving the least satisfactory results (Table VIII). This was probably due to improper selection of cases, as both cases we listed as unsatisfactory had some displacement of the fragments and reduction should have been attempted immediately. After failure, these were treated in a plaster encasement, following an attempt to improve the position of the fragments. Both of these cases eventually obtained a quite satisfactory end-result. Excellent results were obtained in fractures without displacement by injection and early mobilization.

TABLE IX
FRACTURES OF THE CLAVICLE

Case	Age	Fracture	Other Treatment	Injections	Days	Disability*	Result
O D	25	Tip of clavicle	None	1	3		Excellent
M F	23	Tip of clavicle	None	1	2		Excellent
J L	69	Shaft	Plaster Fig of-8	1	5		Good
B S	56	Shaft	Plaster Fig of-8	1	6		Good

* Average period of disability 4 days

FRACTURES OF THE RIBS

Case	Age	Fracture	Other Treatment	Injections	Days	Disability*	Result
W S	60	12th rib	Strapping 2 days	1	7		Fair
N K	51	7th rib	Strapping 2 days	2	2		Fair
M D	53	7th rib	Strapping 11 days	2	14		Good
L G	30	8th rib	Strapping 2 days	1	4		Good
D A	47	7th rib	Strapping, 14 days	2	55		Unsatisfactory

* Average period of disability 16 days

Clavicle and Rib Fractures—Except for two fractures of the tip of the clavicle, injection and mobilization seemed to have little more to offer than

other types of treatment which permit early function. However, our experience was rather limited. Also, fractured ribs did not give as good results as we had anticipated (Table IX). Certainly they are ideal, theoretically, for this form of therapy. Most of these patients were very heavy, and possibly our lack of success should be attributed to improper technic rather than method. A patient who had disability for almost two months was promptly relieved by regional nerve block with procaine and alcohol, as recommended by Rovenstine and Byrd¹¹.

A



B

FIG 8—Fracture of left transverse process, fourth lumbar vertebra. Four procaine injections and adhesive strappings. (A) Roentgenogram 18 days after fracture, early callus. Patient returned to work, as an inspector, on fourth day after fracture. (B) Follow up roentgenogram seven weeks after fracture, no disability.

TABLE X
MISCELLANEOUS FRACTURES

Case	Age	Fracture	Other Treatment	Injections	Days Disability	Result
R G	36	Left transverse process 4th lumbar vert	Strapping	5	11	Excellent
F S	40	Transverse processes 2nd & 3rd lumbar vert	Strapping	3	13	Good
E B	2	Both bones forearm	None		17	Excellent
J M	56	Shaft of fibula	Gelatin boot	1	15	Good

Miscellaneous Fractures—Two cases of fracture of the transverse process of lumbar vertebrae gave excellent results (Table X) This is a fracture

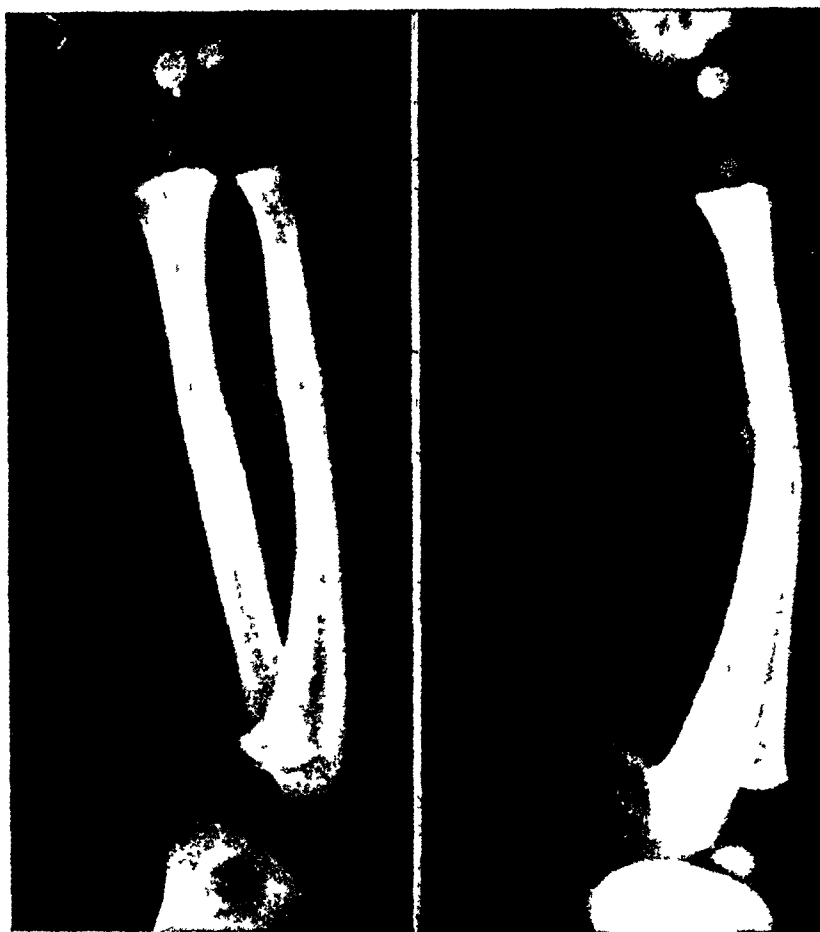


FIG 9—Fracture of both bones of forearm First seen 11 days after fracture Note early callus No immobilization, no injection because patient had no pain Excellent union with slight deformity, normal function

that certainly has been overtreated It is hard to conceive how this fracture can be immobilized under any circumstance, either by bed rest or the application of a plaster encasement The following case illustrates the therapy in these cases

Case Report—On January 5, 1941, a male, age 36, fell, striking the lower back on a block There was tenderness over the third and fourth transverse processes and erector spinae muscles The patient was injected and strapped on January 8, 1941 This was repeated on four occasions, the last injection being given on January 29, 1941 He returned to work the day after the first injection Slight discomfort was present until February 18 Follow-up examination, March 26, showed no symptoms and the patient could move his back in all directions without discomfort (Fig 8)

COMMENT—Callus formation does not appear to have been delayed in these cases. As a matter of fact, one is impressed by the early formation of callus. We wish to cite two cases who were treated only by mobilization.

Case 1—A male, age two and one-half, fell from a scooter on February 7, 1941, injuring both arms. Roentgenograms, February 10, showed a fracture of the external condyle on the left, and of both condyles on the right side. There was no displacement and, in view of the fact that the child was uncooperative and it would have been extremely difficult to adequately immobilize these fractures, the arms were simply mobilized. One week later, the child used the arms without apparent pain. Roentgenograms, February 24, only 17 days after injury, showed excellent callus formation. Final examination, March 3, showed excellent function, although flexion was still slightly limited.

Case 2—A child, age two, fell from a chair, January 12, 1941. The mother treated the arm with applications of Epsom salt. Because of slight deformity in the arm, the child was brought into the hospital. Roentgenograms showed fracture of both bones of the forearm, with callus formation 11 days after injury (Fig 9). The arm was splinted. All splints were removed in five days. Final examination, February 12, showed no pain, tenderness, or discoloration. Slight angulation was present.

From these two cases, one might assume that the most important factor in this method of treatment is mobilization, and one might question whether the procaine has any benefit. There were nine cases in this series which were seen late, an average of 19 days after injury, the shortest time elapsed was ten days and the longest, 50 days. All these cases complained of pain and disability. They were all relieved by procaine injection sufficient to permit resumption of active function. This would tend to prove that mobilization is not the only factor.

SUMMARY AND CONCLUSIONS

The methods employed and the results obtained in 84 fractures treated by this method are reported. The results were unsatisfactory in only four cases, and in no case was the eventual end-result impaired by an attempt at this method of therapy.

Many minor fractures are best treated by early mobilization and procaine injection. The procaine injection at the site of fracture or into the sympathetic ganglia interrupts the reflex which produces vasomotor changes, edema, and pain at the injured site. Early mobilization is thereby permitted, and rapid and excellent fracture healing results. The period of disability is reduced and the eventual end-result is improved in many instances, especially in articular fractures.

Only fractures which do not require reduction in non-weight-bearing bones can be treated by this method.

The author wishes to acknowledge the kindness of Dr Eugene P. Pendergrass, Professor of Radiology at the University of Pennsylvania Hospital, for the roentgenograms used in this study.

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THREE YEARS' EXPERIENCE WITH VITALLIUM IN BONE SURGERY*

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AND

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IN OCTOBER, 1936, we¹ first described the effects of electrolysis on metals in bone and showed by our research that electrolysis was the principal cause of failure of metal appliances in bone. While conducting these experiments, we found only one alloy among all those tested that was completely passive (electrically inert) in the presence of body fluids, that caused no pathologic changes in bone, and that was not itself corroded. This alloy, Vitallium, composed of cobalt, chromium, and molybdenum seemed so inert that we recommended its use in bone surgery. Since then, Vitallium appliances have been widely used over a sufficient period of time to justify a statistical study of the value of this new alloy. Sixty-one surgeons in various parts of the country who have used Vitallium appliances cooperated with us in the following analysis which is based on a total of 1,227 cases.

These 1,227 cases do not include more than 200 patients in whom Vitallium hip cups have been used, or those instances where Vitallium orbital implants were utilized, but are those in which nails, screws, plates, *etc*, were placed in bone to treat various fractures. For fractures of the neck of the femur, 23 surgeons used Vitallium Smith-Petersen nails, two used hip screws, two used lag screws, and three used plain Vitallium nails, without a single case of extrusion of the nails. The 1,227 fractures treated with Vitallium appliances included fresh fractures, old fractures with delayed or nonunion, compound fractures, and old cases where Vitallium screws were used to secure bone grafts. In all these varying conditions, and in the hands of many surgeons, 1,136, or 92.6 per cent of the cases, obtained solid bony union while 47, or 3.8 per cent, had delayed union, and only 44, or 3.6 per cent, developed nonunion. Many of these cases were those wherein there was much trauma or where the fractures were originally compounded.

Vitallium, of course, has no stimulative effect on the healing of bone but it is distinctive among metals in that it has no retarding effect. With such an absolutely nonelectrolytic alloy, it is possible to plate certain fractures or nail fragments securely without fear of erosion of bone about the metal appliances. The permanent immobilization of fragments which can be gained with this inert material insures rapid and solid healing of fractures. Metal nails in the hip have completely revolutionized the outlook for patients with fractures of the neck of the femur and the possibility of union is much greater when

* Presented before the Texas Surgical Society, Dallas, Texas, April 1, 1940

there is no erosion of bone about the metal (Fig 1) Similarly, metal plates are invaluable in other troublesome fractures such as those in both bones of the forearm, the shaft of the humerus, or the upper end of the shaft of the femur

For years, there has been much apprehension about the use of metal appliances in fractures because surgeons have observed many failures after

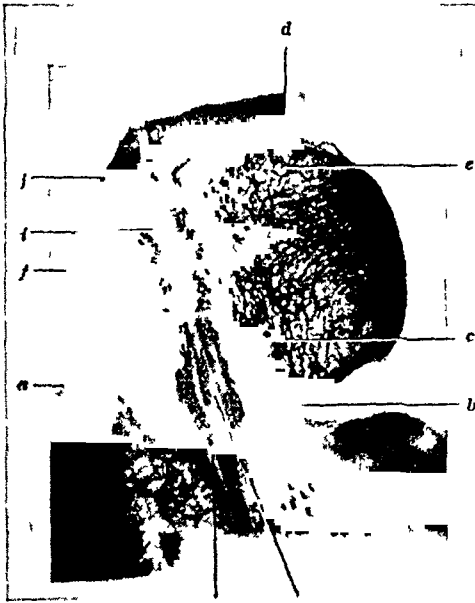


FIG 1—Photograph of neck of the femur where a stainless steel nail has been in the bone about eight months. Note deposits of metal in the head of the bone and absorption of cancellous bone along the path of the nail (From Felsenreich Arch f klin Chir, 195, 30 1939)

they have placed highly electrolytic alloys in the bone. The subsequent electrolytic destruction of metal and bone caused the operations to end unsuccessfully and convinced the surgeons that metals cannot be used in the body with any degree of safety. Loosening of appliances, discoloration of tissues, and accumulations of sterile fluid caused by "electrolytic osteitis" were attributed to infection, faulty technic, or some vague foreign body irritation.

Failures with Vitallium Appliances

—The original dental Vitallium alloy, with which we first experimented, was found to be too brittle and weak for fracture work. Shortly after we recommended its use in surgery, other surgeons also complained of the same defects in the material. Consequently, at our suggestion, the manufacturers of Vitallium modified the structure of the alloy to give it strength and toughness while retaining its remarkable passivity in body fluids.

Even so, for all the early cases with broken plates and screws, they constitute but a very small per cent of the successes with Vitallium appliances. Out of 1,227 cases, of all types, there were 11 instances in which a plate broke, or 0.089 per cent of the total. Ten screws broke, or 0.081 per cent of the total. Four plates bent, or 0.033 per cent of the total. Two nails bent, or 0.016 per cent of the total. One hip screw bent, or 0.008 per cent of the total. In other words, 1,199 of the cases, or 97.7 per cent of the total, had no technical trouble from the application of the metal.

Bent or Broken Plates—In 1937, the first year Vitallium was generally used, several surgeons found that plates bent or broke even though the extremity was well supported externally. In these instances, the metal was at fault because it was too brittle at the outset. Also, the early flat plates were made too light and the Lane-type plates were too narrow. This has now been corrected by making heavier appliances of Vitallium more malleable,

so that plates may be bent to fit an irregular surface without danger of breaking and they will not bend or break if an extremity is handled with reasonable caution

Of course, no Vitallium or any other metal plate is strong enough to immobilize a fractured long bone without additional external support by plaster encasement or splint. Unless adjacent joints are immobilized by such splints, there is always the possibility that the fragments may move or that some undue strain will detach the appliance from the bone. The tensile strength of a nail, screw, or plate is not an important factor since it is only called upon to hold bone fragments together in normal alignment. The support of the entire extremity and the protection against muscle pull must be provided by plaster encasements and splints in addition to the plates attached to the bone.

Screws which erode bone by "electrolytic osteitis" are like screws in decaying wood that lose their hold and thus fail in their purpose. Just as it is important to keep screws and wood dry to prevent loosening, so is it necessary that screws in bone must be nonelectrolytic to prevent erosion of bone. Consequently, no metal plates and screws are absolutely dependable for immobilizing fractures unless they are totally passive (nonelectrolytic) in the body.

Vitallium is so hard that plates, nails, and screws must be cast and this process is costly. Its strength is not as great as some of the stainless steels but it possesses, in its present composition, all the strength needed to immobilize bone fragments which are properly supported externally. Certainly, an alloy which is absolutely passive, and hence nonirritative, and which can be used by many surgeons with 97.7 per cent success, fulfills the requirements of an almost perfect material for the internal fixation of fractures.

Bent or Broken Screws—The first Vitallium wood-type screws were made with a thin shank which was too fragile and which broke quite easily (Fig 2). This has been corrected by making a heavier screw of tougher metal and with a stronger shank. The screws with threads which extended to the head were

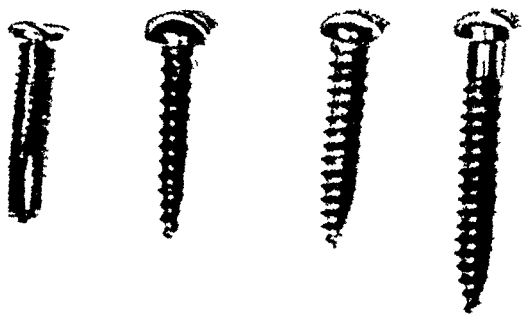


FIG 2—Photograph of various types of Vitallium screws. (Machine type screw which cuts its own thread in the bone. First wood type screw with too small a shank. Newer wood type screw with threads to the head for use with plate. Wood type screw with smooth shank for tightening fragments.)

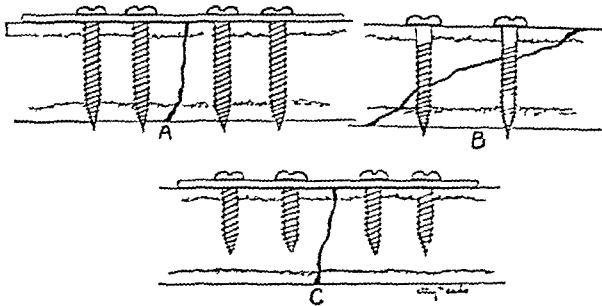
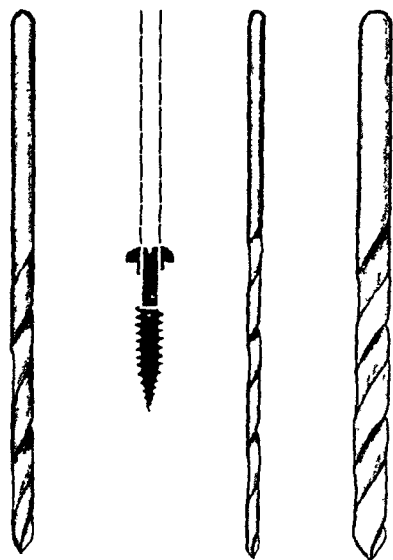


FIG 3—Diagram of bone with plate and screws inserted. (A) Long screws engaging both cortices giving best support. (B) Screws with unthreaded shank used to pull oblique fracture together. (C) Short screws engaging only one cortex.

designed for use with a plate, while those in which part of the shank was unthreaded were made for pulling fragments together. Naturally, if the former type of screw is used for this purpose the drill-hole in the proximal fragment must be larger than the diameter of the thread. Improper screws

Correct size Shank of screw Too small Too large



Betty Bebb's Co.

FIG 4—Diagram demonstrating correct size of drill to use in making screw hole. Drill must be exact diameter of the shank of the screw.

or those used incorrectly would naturally tend to break (Fig 3). Many surgeons complained of difficulty in using the machine-type screws with the cutting edge which is supposed to make a path for the thread in the bone. When such a screw is cast of Vitallium, the thread is not sufficiently sharp to cut the bone easily. Also, such screws, without a taper point, are difficult to insert. Therefore, we feel that the machine-type screw of Vitallium is not nearly so successful as the plain wood-type or coach-type screw. A rather obvious cause of failure in placing screws in the bone is disproportion between the size of the screws and the caliber of the hole in the bone (Fig 4). The drill-hole should have exactly the same diameter as the shank of the screw. If the hole is larger than the shank, the threads do not engage deeply enough in the bone to secure a good purchase and the threads are easily stripped when the screw is finally tightened. If the hole is smaller than the shank, great force is required to drive the screw home and this causes slipping of the screw driver, breaking of the head of the screw, or inability to tighten the screw against the plate.

Another common cause of failure in inserting screws in bone is carelessness in the depth of the holes drilled. Even if a screw is not long enough to pass through both cortices of the bone, the hole should be drilled deep enough so that the tip of the screw does not strike bone. It is a safe rule to drill holes through the entire bone so that the screws have ample clearance. Longer screws provide stronger support than shorter screws and screws which engage both cortices of a long bone provide better anchorage than screws in one cortex alone. If long screws are used, holes should pass entirely through the bone to permit the ends of the screws to project on the opposite side.

Should Vitallium Appliances Be Removed?—While we ordinarily do not remove Vitallium appliances after fractures have healed, some surgeons prefer to because they hesitate to leave "foreign material" in a bone. This atavistic idea originates from the old fear of irritative reactions about metals in the

body Previously, metals were used which caused "electrolytic osteitis" of bone with occasional breaking open of wounds, draining sinuses, and in some cases, late fracture Vitallium, which causes no reaction at any time, can be left indefinitely in the body with no danger of late tissue damage It has been pointed out that many old metal appliances or pieces of metal have been left in the body for years without causing symptoms This is true but it is probably due to the fact that these metals became encapsulated in dense fibrous tissue which prevented body fluids from coming in contact with them, or they developed a protective molecular veil ("oxygen film") which reduced electrolytic activity In any case, wounds have healed in spite of their presence

In this series of 1,227 cases, Vitallium appliances were removed in 87 instances after the bone was healed and the need for them no longer existed Every observer reported that the screws and plates were bright and untarnished and that the tissues about them were normal in appearance Where

there was no infection or other complications, the screws were tight in the bone and force was required to remove them In other words, there was no evidence of the slightest erosion of bone or of any irritation of soft tissue from the presence of the Vitallium metal In general, roentgenograms of the Vitallium appliances revealed no changes in the bone about the metal at any time after they were inserted As Smith-Petersen remarked, "Vitallium seems to be as inert in the body as a piece of glass" Others stated "Vitallium causes the least irritation of any metal we have ever used", or "even in soiled bone the soft parts healed around the plates in an astonishing manner"

Infected Wounds—Of these 1,227 operations, where Vitallium was used, 55, or 0.044 per cent, were followed by infected or draining wounds Of these, 46 were cases of severely compounded fractures that had been plated, one was a relighting-up of an old infected hip, and one was in a patient with phlebitis and cystitis In the remaining seven cases, each surgeon stated that

FIG 5

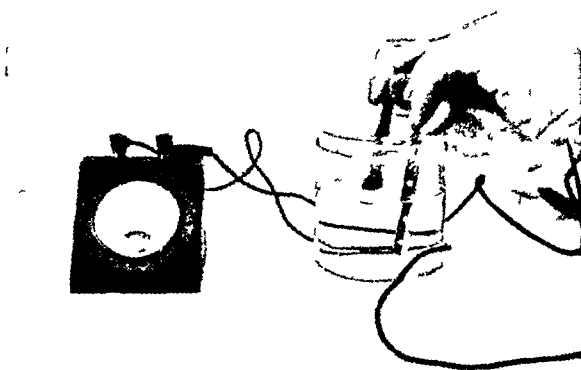
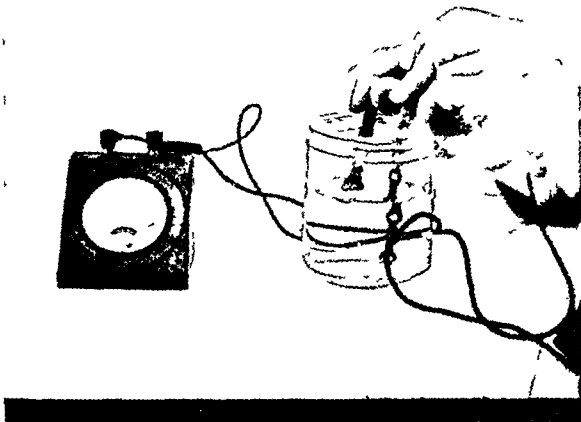


FIG 6

FIG 5—Photograph of micro ammeter coupled with stainless steel plate in saline solution Note that maximum current is produced

FIG 6—Photograph of micro ammeter coupled with Vitallium plate in saline solution Note that no current is produced and the micro ammeter registers zero

the subsequent infections were "not attributable to the metal" and that when screws were loose it was due to the infection

Vitalium appliances not only did not cause infections in the bone but, in several instances, infected wounds gradually healed around the metal. Many surgeons, including ourselves, have applied Vitalium plates to fresh compound fractures and have seen the fractures and skin wounds heal by first intention. This advance in fracture treatment has done much to prevent the usual deformities and delayed unions after compound fractures.

CONCLUSIONS

(1) Metals which are nonelectrolytic (passive) in body fluids cause no pathologic reactions in the tissues. Vitalium which is completely passive is more inert than any alloy that has been developed so far.

(2) 1,227 Vitalium appliances used by 61 surgeons, in various parts of the country, resulted in 92.6 per cent solid bony union of fractures, 3.8 per cent delayed union, and 3.6 per cent nonunion.

(3) When Vitalium was first introduced, it was not strong enough or sufficiently malleable for general use. These defects have been corrected. In spite of former faults in the material, breaking of plates and screws occurred only 28 times in a series of 1,227 cases, or only 2.3 per cent of the total. This percentage has steadily decreased as the alloy has been improved.

(4) Screws made of Vitalium were originally too fragile for all uses. The new screws are amply strong for any type of operation and the wood-type screw has been found to be most satisfactory.

(5) On the occasions when Vitalium appliances have been removed, the surrounding bone has shown no erosion or discoloration.

(6) When infections occurred in any cases in this series, they could be traced to such causes as compound injuries, septicemia, etc. In other words, no wound became infected *because* of a Vitalium appliance.

(7) On the basis of this study, it has been found that Vitalium has sufficient strength and inertness to be perfectly suited to all requirements of bone surgery.

(8) In metals or alloys the phenomena of passivity are apparently closely linked to their degree of inertness under corrosive conditions, and comparative determinations of current flow with a micro-ammeter, using some common third metal as an anode, give useful indications of their probable tendencies toward reaction *in vivo*. Metals or alloys that give relatively high readings are likely to cause a corresponding disturbance in bone or tissue. Above all, two metals or alloys of different character must be avoided, such as a plate of one kind and screws of another, in the same operation.

(9) In any new metal, tensile strength, hardness, shape of appliances, etc., are all comparatively unimportant and secondary to the vital fact that the material must be passive (nonelectrolytic) in the tissues.

(10) A great deal of study and development is going on in the field of

stainless alloys The theoretical work of Uhlig and Wulff at M I T has thrown additional light on passivity, and disclosed the limitations of the oxide film protection theory This newer conception which deals in terms of the structure of the atomic lattice shows, more rationally, the importance of the rôle of hydrogen in the loss of passivity and explains why the addition of molybdenum to the 18-8 type of material, has increased its resistance to corrosion attack, particularly of the localized form resulting in pits Maybe it is possible that further developments will produce material more suitable than the best of the present available stainless steels

(11) We will continue our search for an ideal alloy for use in the body and enlist the aid of chemists and metallurgists to help discover such an alloy We hope some material can be discovered which has the proper strength, ductility, and passivity for all uses in the body So far, Vitallium is the only metal we have found which is completely passive in body fluids The final choice of material must possess such complete passivity

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BRIEF COMMUNICATION

A SIMPLIFIED ARTHROMETER

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FOR SIMPLE and more accurate measurement of joint position and motion, the writer, for several years, has employed the pocket instrument illustrated in Figure 1. The construction is such that the indicator retains a fixed horizontal position, and rotation is directly denoted in degrees on the graduated dial face. The operation and application of the instrument will be obvious from the illustrations. It can be applied to virtually every position and motion of the body, and has been useful in estimating obliquities of the pelvis, shoulders, and trunk (Fig 2).

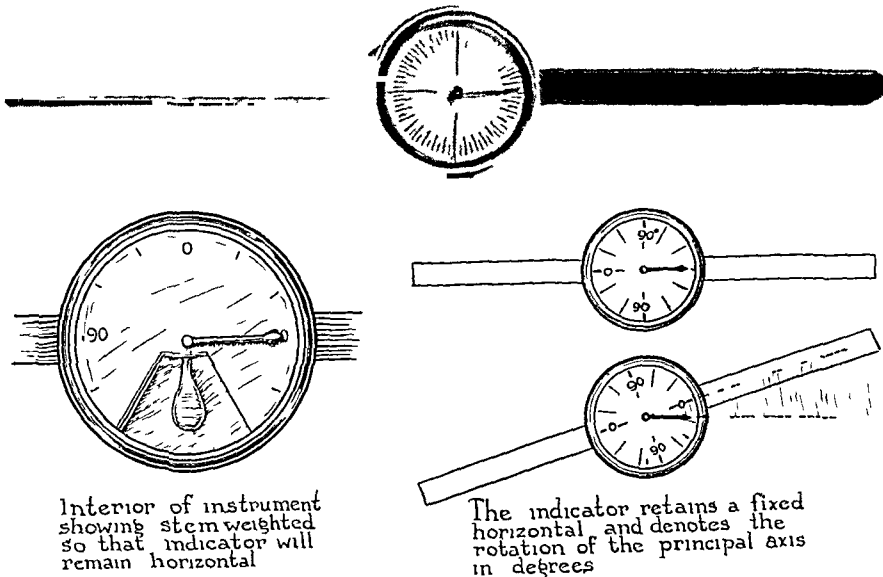


FIG 1

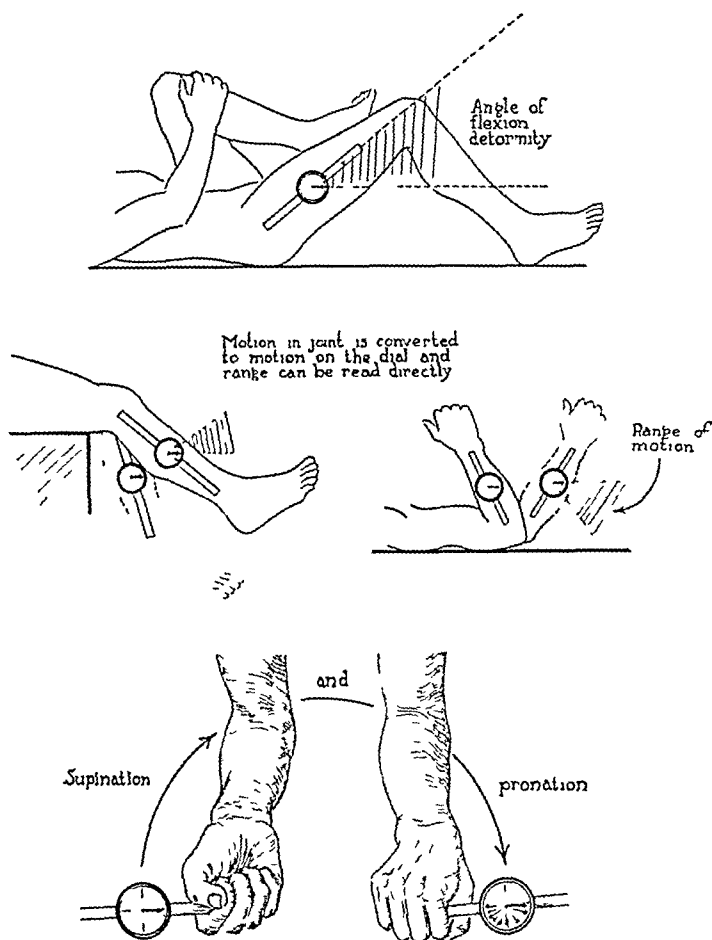


FIG 2

BOOK REVIEWS

OPERATIVE SURGERY By J SHELTON HORSLEY, M D, LL D, F A C S, Richmond, Va, and ISAAC BIGGER, M D, Richmond, Va St Louis, Mo C V Mosby Co

THIS is the Fifth Edition of a standard textbook of "Operative Surgery" by Doctors Horsley and Bigger, which was first published in 1921. But three years have elapsed since the appearance of the Fourth Edition, but no one will take issue with the authors' statement that such rapid progress is now taking place in surgery that a revision at this time was indicated. As in the Fourth Edition, the book appears in two volumes, which are a credit to the publisher and add new laurels to the illustrator, Helen Lorraine.

In the preface one finds outlined the newer procedures which have been added, such as ligation of the patent ductus arteriosus, segmental pneumonectomy, and extrapleural pneumothorax. But this does not speak of the careful reediting which is evident upon almost every page of the book when one compares it with the previous edition.

The chapter on peritonitis has been almost completely rewritten and now occupies 28 pages, and there has been a similar editing of the chapter on appendicitis, which is very greatly expanded.

In this work they still carry a section on orthopedics, which is gradually being deleted from the textbooks on general surgery, and while it maintains its former high standard, the accepted technics of practically all the newer procedures in orthopedic surgery are now included.

The illustrations throughout the entire book maintain the uniform perfection which has been so characteristic of this textbook from its First Edition, and these illustrations are a great asset to those of us who are more visually minded than word minded

That the authors have accomplished their objective, and have brought this long recognized standard textbook of "Operative Surgery" up to date will be evident to any one fortunate enough to possess a copy

All concerned in the reediting of this work are to be congratulated upon this addition to our surgical literature

WALTER ESTELL LEE, M D

DISEASES OF THE ESOPHAGUS By PORTER B VINSON, M D, Professor of Bronchoscopy, Esophagoscopy and Gastroscopy, Medical College of Virginia Springfield, Ill
Charles C Thomas Co, 1940

VINSON, in a monograph on diseases of the esophagus, presents, for the first time, a discussion of the diagnosis and treatment of esophageal lesions in book form. The need for such a book becomes apparent when one considers the variety of conditions which are overlooked at the present time, and when prepared by one with such experience in this specialty, it can be accepted as authoritative, and should provide a useful guide not only for the specialist, but also for the general practitioner. It would seem to the reviewer that this is just what Vinson has accomplished.

The book, as all products of the publishers, Charles C Thomas Co, is worthy of the text, with its clear, large type, excellent illustrations, and a generous use of line drawings which serve to supplement unusually well-reproduced roentgenograms and photographs.

The table of contents starts with the general management of the patient, and in 16 chapters adequately covers the subject, concluding with an evaluation of the present status of gastrostomy.

Among the highlights are the discussions of the congenital, malignant and traumatic lesions, the various diseases, and the foreign bodies which one should consider in patients who experience difficulty in swallowing.

A carefully made and not too fulsome bibliography at the end of each chapter is a real asset to the text.

Specifically, the author emphasizes the fact that 90 per cent of lesions of the esophagus may be accurately diagnosed without the use of the special examinations and instruments which he discusses, and he warns against the danger of stressing the importance of these special procedures, making a plea for a careful routine general examination, which, in addition to making unnecessary special examinations in a large number of cases, should always be coordinated with the special procedures.

He very properly calls attention to the fact that marked emaciation associated with esophageal obstruction is not necessarily due to malignancy, but very frequently is the result of starvation and dehydration only. Further, as a result of the dehydration which follows esophageal obstruction of any kind, surgical procedures are followed by a very high mortality rate, averaging 50 per cent. This, however, may be lowered if the required fluids are provided preoperatively. He claims gastrostomy should never be considered as a minor procedure, for it is followed by an unexplainable mortality—10 to 15 per cent, and should always be preceded by putting the patient in water and electrolyte balance preoperatively. In addition to the mortality rate, it carries a hospitalization of from 10 to 14 days. Further, he is very pessimistic about the results that may be expected in gastrostomy, and claims it is not palliative in malignant obstruction, while in benign obstruction the stricture may become complete, unless routine dilatation is carried

on, which is made possible by the swallowing of a string which will act as a guide for the passage of a sound

It is startling to read that in approximately 40 per cent of patients suffering with difficult swallowing, the obstruction is the result of carcinoma, which in approximately 5 to 7 per cent of all carcinomatous lesions involves the esophagus. No exception can be taken to his claim that an accurate diagnosis of malignancy can be made only by biopsy, and then by a pathologist who is experienced in the handling of small pieces of tissue, but we cannot fully agree with his pessimistic attitude about the value of gastrostomy in hopeless malignancy, especially in those cases in which it is impossible to pass a stomach tube through the lumen of the obstructing growth. In our experience, approaching death has not been so horrible when we have been able, with a gastrostomy, to avoid the throes of starvation and thirst.

The subject of esophageal diverticula is given due consideration, and the value of the guidance provided by the swallowed string is emphasized. With this procedure a catheter can usually be guided past the opening in the lateral wall of the esophagus into the sac. This is the procedure which has been employed by Jackson for many years and is one of the basic principles of his use of the esophagoscope in the one-stage operation. Vinson, however, seems to be unable to decide between the prehistoric two-stage operation of excision, which was first advocated by Moynihan, and the one-stage procedure which has been made possible by Jackson's cooperation with the esophagoscope. Those who have had experience with the one-stage technic are definitely convinced that this procedure is applicable in all types of pulsion diverticula, provided the esophageal lumen can be maintained during the process of isolation of the sac, and that angulation of the esophageal wall is prevented. Such protection, in our experience, can be supplied only with the esophagoscope or a stiff stomach tube.

The future of gastrostomy, Vinson feels, is now assured, but for the present, at least, we must consider that direct visualization of the lining of the stomach is but one method of diagnosis—and we would like to add that it should be correlated with other accepted routine diagnostic procedures. He wisely warns that a negative gastroscopic examination is of little value—and again we add that a positive one should be in agreement with other clinical findings in order to be accepted at par value. His inclusion of this subject, and the limited space devoted to it, would seem to merely emphasize its possibilities, and he very properly refers his readers to Rudolph Schindler's book on "Gastroscoy" for an adequate presentation of this field.

WALTER ESTELL LEE, M D

ABDOMINAL OPERATIONS By Rodney Maingot, F R C S, England, 2 vols, 8°, pp 1385 Appleton-Century, New York and London, 1940

Mr Maingot's work is not restricted to a consideration of operative technics. The two volumes cover the surgical problems of the abdomen with the same completeness of detail found in many of the longer systems of surgery. Incidence, classification, pathology, etiology, diagnosis, pre- and postoperative care and prognosis are discussed almost as fully as operative technic. Important references are conveniently cited in the text.

As with most texts by individual authors, some sections are more brilliantly written than others. The section on liver abscess seems particularly well done. In the section on appendicitis nearly all phases of the disease are thoroughly discussed except for the postoperative management of patients with spreading peritonitis. This subject, which is the crux of the problem of appendicitis mortality, is all but omitted. The important subject of chemotherapy is not adequately discussed either in relation to appendicitis or to colon resections. The use of the Miller-Abbott tube is mentioned but the technic of its use is omitted and the indications and contraindications for its employment are not considered in appropriate detail.

Despite these omissions, however, the work as a whole is comprehensive and a high standard of conciseness and clarity is maintained both in the text and in the illustrations. It should be very useful for those who require a thorough discussion of the general surgical problems of the abdomen without requiring a complete system of surgery.

JONATHAN E. RHOADS, M.D.

CORRESPONDENCE

THE EDITORIAL BOARD, ANNALS OF SURGERY,
J. B. LIPPINCOTT COMPANY,
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Dear Sirs:

June 23, 1941

It has been brought to my attention that, in discussing a paper read by Dr. Wm. F. MacFee on "Hernia" at the annual meeting of the American Surgical Association held in St. Louis in 1940, I misquoted Doctor Burdick and Doctor Coley to the effect that they had stated that they had failed to master the technique of using fascia and had suggested as a substitute the removal of the testis and spermatic cord. This I regret exceedingly as their papers show that no such interpretation of their statements was justifiable. I shall be very glad indeed if you will give this note the publicity necessary to counteract any misconception of their views that my remarks may have caused.

Yours sincerely,
W. E. GALLIE, M.D.

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EXPERIMENTAL CEREBRAL TRAUMA

III THE EFFECTS OF ACUTE UREMIA, OF VENOUS OBSTRUCTION, OF HYPERTHERMIA, AND OF INTENSIVE IRRADIATION ON THE WATER CONTENT OF THE DOG'S BRAIN

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AND

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IN PREVIOUS EXPERIMENTAL STUDIES,^{1 2} it has been found that the water content of the dog's brain is remarkably constant in normal animals. Further, no significant alteration in the water content of cerebral gray or white matter, cerebellar gray matter or the brain stem was produced by trauma to the head, even though the trauma was sufficiently severe to produce a marked elevation in cerebrospinal fluid pressure, and even though in some experiments a portion of the skull and dura mater was left open to allow free expansion of the brain. The findings in these previous experiments are summarized in Table VII.

The series of experiments to be reported in this paper were undertaken to determine whether the water content of the brain was altered in other conditions which have been reported to be associated with "cerebral edema." The conditions studied were acute uremia, obstruction of the superior vena cava and azygos vein, severe fever, and intensive irradiation of the head.

Methods and Results—Dogs were used in all experiments and the same methods of study of the water content of the brain were employed as in the previously reported experiments.^{1 2} The animal was sacrificed by stabbing the heart. The brain was removed and specimens of cerebral gray and white matter, cerebellar gray matter, and brain stem were obtained by the same individual (C. P.) and by the same technic in all experiments. Specimens were weighed immediately (seven to ten minutes after death) and dried to constant weight at 60° C.

Group I—Acute Uremia Bilateral nephrectomy was performed in six

and bilateral ureteral ligation in five animals, under nembutal anesthesia. Such animals go into prompt and profound uremia.³ They were sacrificed by stabbing the heart in the moribund period two to five days after operation. In the nephrectomy group, mean arterial blood pressure was determined with the animal at rest before operation and immediately before sacrifice by means of a needle inserted into the femoral artery and communicating with a mercury manometer. Blood nonprotein nitrogen was determined at the same time in both groups, the eyegrounds were examined, and the cerebrospinal fluid pressure determined* by means of a needle in the cisterna magna immediately before the animals were sacrificed.

TABLE I
THE EFFECTS OF BILATERAL NEPHRECTOMY

Dog No	Days After Operation	Mean Blood Pressure		Blood Nonprotein Nitrogen		Percentage of Water in Brains			
		Control Mm Hg	Immediately Before Sacrifice Mm Hg	Control Mg Per Cent	Immediately Before Sacrifice Mg Per Cent	Cerebral Gray Matter	Cerebral White Matter	Cerebellar Gray Matter	Brain Stem
E1	3	160		34	109	80.0	64.4	80.6	71.8
E2	2	160	110	31.5	109	79.7	64.1	79.5	70.3
E3	2	120	90	30	110	79.7	68.2	79.0	71.3
E5	2	100	90	31		78.6	66.8	79.2	70.6
E6	3	80	80	32	114	79.2	67.0	79.3	72.0
E7	3	60	50	30	112		69.2		71.0
Averages						79.4	66.6	79.5	70.2

All animals subjected to bilateral nephrectomy exhibited lethargy and drowsiness progressing into deep stupor. They took little or no water. None had convulsions or other symptoms referable to the nervous system. Other findings are given in Table I. The blood pressure diminished from 160 to 110 Mm in one animal, and remained essentially unchanged in the remaining experiments. The blood nonprotein nitrogen was greatly elevated in five cases† at the termination of the experiments. The brain appeared normal in all animals except Dog E6, in which it seemed somewhat shrunken after the dura was opened. Values for the water content of cerebral and cerebellar gray matter and brain stem were remarkably constant. Those for the cerebral white matter were more variable and were definitely lower than average normal figures in two experiments (Dogs E1 and E2). Average values, however, were very close to normal averages (Table VII).

The animals in which both ureters were ligated were sacrificed after three to five days. Two exhibited convulsions and two vomited frequently. None drank water after the first day. The blood nonprotein nitrogen was

* The needle was connected directly with a water manometer. With the head slightly elevated and the neck flexed anteriorly, cerebrospinal fluid normally barely appears in the manometer. Any measurable rise in the tube was assumed to be an elevation of pressure above the normal.

† The blood specimen from Dog E5 clotted and was discarded.

over 200 mg per cent in all cases and the cerebrospinal fluid pressure was slightly elevated in two animals (Table II) The brains were grossly normal The water content of the cerebral gray matter was slightly but consistently lower than the normal value That of the cerebral white matter was somewhat variable and was definitely low in two animals The other values were consistently normal

TABLE II
THE EFFECT OF BILATERAL URETHRAL LIGATION

Dog No	Days After Operation	Findings Immediately Before Sacrifice			Percentage of Water in Brains			
		Blood N P N Mg Per Cent	CSF Pressure (Cisternal)	Optic Disks	Cerebral Gray Matter	Cerebral White Matter	Cerebellar Gray Matter	Brain Stem
E26	5	200	±	Normal	77.6	65.7	78.3	71.4
E27	3	250	±	Normal	78.5	67.9	79.8	70.7
E28	3	205	±	Normal	78.7	67.0	78.6	70.1
E29	3	230	>10 Mm increase	Normal	78.3	66.5	80.8	71.4
E30	3		>10 Mm increase	Normal	78.6	63.6	78.8	69.2
Averages					78.3	66.1	79.3	70.6

COMMENT—The neurologic symptoms occurring so frequently in uremia have long been attributed to “cerebral edema” Rees⁴ and Traube⁵ believe that cerebral edema was the cause of such symptoms, and Volhard⁶ postulated an “acute false uremia” which he thought due to cerebral edema Fishberg⁷ states that this cerebral edema is the result (and not the cause) of “hypertensive encephalopathy,” with or without uremia Blackfan^{8, 9} has repeatedly emphasized the presence of cerebral edema in uremia in children

The “acute” experiments reported above are not directly comparable to such clinical states, but they serve to cast doubt upon the occurrence of increased cerebral tissue fluid in acute uremia The low fluid values found in some of our experiments may be the result of vomiting and fluid deprivation

Group II—Venous Obstruction In four dogs, the superior vena cava was ligated, and in four others, both the superior vena cava and the azygos vein were ligated Operations were performed under intratracheal, positive pressure, ether anesthesia In the former four experiments, the animals were sacrificed two to 14 days after operation In the latter, the animals immediately became very ill and were sacrificed 24 to 36 hours after operation Cerebrospinal fluid pressure was measured by means of a needle in the cisterna magna (with the head in the same position as in previous experiments), and the eyegrounds were examined before sacrifice Complete necropsy, in addition to removal of brain specimens, was performed after death In all cases, the ligatures had been properly placed and the venous obstruction remained as intended The animals were sacrificed and specimens of brain tissue were removed and studied as before

When the superior vena cava alone was ligated, the animals showed little general or local effect In two of the four experiments, a moderate effusion of serosanguineous fluid occurred in the right pleural cavity Edema of the

scalp and papilledema did not occur. The water content of the brain closely approximated normal values except for some variations in the cerebral white matter (Table III)

TABLE III
THE EFFECTS OF LIGATION OF THE SUPERIOR VENA CAVA
Percentage of Water in Brains

Dog No	Time of Sacrifice Days After Operation	Cerebral Gray Matter	Cerebral White Matter	Cerebellar Gray Matter	Brain Stem
E13	2	80.3	65.7	80.3	71.6
E12	7	80.0	70.0	80.1	71.6
E11	7	79.5	66.1	80.2	70.4
E15	11	80.3	70.8	76.2	73.2
Averages		80.0	68.2	79.7	71.7

On the other hand when both the superior vena cava and azygos vein were ligated, profound alterations in the animals' general condition were observed. It was necessary to sacrifice them at the end of 24 hours (three dogs), or 36 hours (one dog), because of extreme apathy or stupor and impending death. There was marked edema of the scalp (with subperiosteal hemorrhage in one instance). The optic disks were very hyperemic in one dog, and frankly choked in two others. No retinal or intracranial hemorrhages were observed. The cerebrospinal fluid pressure was elevated in all experiments, the smallest elevation being 20 Mm., the largest 125 Mm. of water. In one animal, a large amount of milky fluid filled the pleural cavities*.

Brain water values are shown in Table IV. In one animal (Dog E16), the water content of the cerebral and cerebellar gray matter was elevated significantly. In the remaining instances, all values were approximately normal, as were the averages.

TABLE IV
THE EFFECTS OF LIGATION OF THE SUPERIOR VENA CAVA AND AZYGOS VEIN
Percentage of Water in Brains

Dog No	Time of Sacrifice Days After Operation	Cerebral Gray Matter	Cerebral White Matter	Cerebellar Gray Matter	Brain Stem
E16	1	82.2	70.7	81.1	72.2
E17	1	79.2	69.0	79.3	71.5
E18	1	79.1	68.7	79.7	70.0
E19	1½	79.2	66.2	79.4	69.2
Averages		79.9	68.6	79.9	70.7

COMMENT—Although the superior vena cava has been experimentally ligated by several investigators,^{10 11 12} the cerebral effects of the procedure have not been studied. That clinical neurologic symptoms may result from obstruction of the superior vena cava (by tumors, aneurysms, etc.) has long been recognized. These symptoms were attributed merely to venous stasis

* Similar chyle-containing fluid has been found in the pleural cavities of cats after ligation of the superior vena cava by Blalock and his associates.^{10 11}

by Phillips,¹³ and Lilienthal,¹⁴ but Ehrlich Ballon and Graham¹⁵ stated "The venous stasis may also cause cerebral symptoms because of edema in the meninges and brain substance" The brain was not examined in the necropsy reported by the last-named authors Waterfield¹⁶ reported marked elevation of the cerebrospinal fluid pressure in a patient with clinical evidence of obstruction of the superior vena cava

No direct observations of cerebral edema in the presence of distant venous obstruction have been found in the literature The high venous pressure which produces edema of the scalp papilledema and elevated cerebrospinal fluid pressure might well be expected to produce edema of the brain as well However no evidence of such edema was found

An increased intracranial blood volume must certainly have existed in these experiments and this could account for the elevation of intracranial pressure The observations of Shapiro and Jackson¹⁷ which were discussed in the preceding paper in this series² are of interest in this connection These authors believe that the increased pressure resulting from cerebral trauma is due to increased intracranial blood volume (intravascular and extravascular) This possibility was also suggested in the first paper of this series¹

Group III—Fever In four experiments, the dogs were placed in an hyperthermic chamber the temperature of which was maintained at 48–52° C They remained in the chamber one to one and one-quarter hours Specimens of brain were obtained as usual immediately after removal

All animals were severely prostrated by the time of removal from the hyperthermic chamber Panting was marked and salivation very profuse in all instances Rectal temperature on removal was 44.4° to 45.5° C (112° to 114° F) Dogs E8 and E9 had generalized convulsions one and one-quarter hours after being placed in the chamber and expired suddenly when removed immediately afterward Dogs E10 and E11 also had repeated convulsions before removal, but were removed and sacrificed one-quarter hour sooner The cerebrospinal fluid pressure was normal in both animals immediately after removal At necropsy the brains presented no visible abnormality *

The brain fluid findings are shown in Table V The percentage of water in both cerebral and cerebellar gray matter, and in the brain stem was consistently higher than normal in all experiments In the cerebral white matter, the percentage of water was within normal limits

COMMENT—In 1918, McKenzie and LeCount¹⁸ reported an increase in the water content of the brains of patients dying of heat stroke Objections to the validity of these findings have previously been mentioned¹ Numerous other authors have reported finding cerebral edema in patients dying of heat stroke or following artificial fever therapy (Lichtenstein¹⁹ Watts²⁰ Hartman,²¹ Schnabel and Fetter,²² and Chunn and Kirkpatrick²³)—but these findings are based on the gross and microscopic appearance of the brains

* "Petechial hemorrhages" noted in the protocol of one experiment proved to be blood vessels (distended?) on microscopic study

and not on water determinations. In their report of a careful experimental study, Hall and Wakefield²⁴ did not report gross edema. Microscopically, they found swelling of the cytoplasm of glial cells.

TABLE V
THE EFFECTS OF HYPERTHERMIA

Dog No	Temp of Hypertherm	Rectal Temp on Removal	Hours in Hypertherm	Percentage of Water in Brains			
				Cerebral Gray Matter	Cerebral White Matter	Cerebellar Gray Matter	Brain Stem
E8	48° C	44.4° C	1 1/4	80.3	67.6	80.4	72.3
E9	48° C	45.0° C	1 1/4	81.3	66.1	81.3	72.8
E10	52° C	45.0° C	1	80.1	67.0	80.7	71.7
E11	52° C	45.5° C	1	82.6	67.8	82.4	73.2
Averages				81.1	66.7	81.2	72.5

In our experiments, the uniformly high values for water content of cerebral and cerebellar gray matter and brain stem seem to us to be significant. It is thought justifiable to conclude that true edema of these portions of the brain results from extreme hyperpyrexia.

Group IV—Intensive Irradiation of the Head. In six experiments, deep roentgen radiation was administered to the entire head. A dosage of 3,000 roentgen units (with backscatter) was delivered in each animal.* The animals were sacrificed at the end of 24 hours in two experiments, 48 hours in one experiment, 21 days in two experiments, and 90 days in one experiment. The eyegrounds were examined and cerebrospinal fluid pressure determined immediately prior to sacrifice.

In the two animals sacrificed one day, and the one sacrificed two days after irradiation, no significant abnormality was noted in appearance of the scalp, optic disks or brain. The cerebrospinal fluid pressure was slightly elevated (less than 10 Mm H₂O) in one experiment (Dog E25), but not at all in the other.

In the animals sacrificed after longer intervals, the scalps were ulcerated and edematous, but the optic disks and brain were not abnormal in appearance. In Dog E24, an elevation of cerebrospinal fluid pressure of less than 10 Mm of H₂O was noted.

The percentage of water in the brain specimens varied somewhat more than usual in the individual experiments (Table VI), but the average findings showed no significant variation from normal values.

COMMENT—The production of edema by irradiation therapy of brain tumors has long been assumed. The literature on this subject was summarized by Bailey, Sosman, and Van Dessel,²⁵ and the danger of edema has more recently been reiterated by Alpers and Pancoast.²⁶ In describing the effects of experimental radium implantation in the brains of dogs, Pendergrass,

* We are indebted to Dr. Herbert Francis, of the Department of Radiology, for administration of the radiation and for the following description of technic: 200 kv, 20 ma, 50 cm distance, 1/2 Mm Cu, 1 Mm Al filters.

Hayman, Houser and Rambo²⁷ stated "The brain shows a general swelling throughout the entire radiated hemisphere, which must be ascribed to the production of an edema which is not limited to the radiated area, but extends throughout the entire hemisphere"

TABLE VI
THE EFFECTS OF INTENSIVE IRRADIATION OF THE BRAIN

Dog No	Time of Sacrifice Days After Irradiation	Percentage of Water in Brains			
		Cerebral Gray Matter	Cerebral White Matter	Cerebellar Gray Matter	Brain Stem
E23	1	79.3	65.6	79.9	70.8
E25	1	81.4	67.9	81.1	70.2
E20	2	77.0	64.4	78.2	70.0
E21	21	79.0	68.8	79.6	70.6
E22	21	77.4	64.2	78.5	69.3
E24	90	79.9	69.0	79.0	72.1
Averages		79.0	66.6	79.4	70.5

Under the conditions of our experiments, no increase in the water content of the brain resulted from intensive irradiation of the head. The unfavorable symptoms which undoubtedly sometimes follow roentgenotherapy may be due to changes in such factors as blood volume, cerebrospinal fluid balance or to actual hemorrhage (as suggested by Bailey, Sosman, and Van Dessel²⁵).

The findings in the experiments here reported again demonstrate the remarkable stability of the water content of the dog's brain, both in corresponding specimens from a single animal (*e.g.*, cerebral and cerebellar gray matter) and from different animals under widely varying abnormal conditions.

For purposes of comparison, a composite tabulation of the average findings in these and previously reported groups of experiments is given in Table VII. Only the group subjected to high fever showed a consistent elevation in brain water content.

TABLE VII
COMPOSITE TABLE OF AVERAGES

		Percentage of Water in Brains					
Type of Experiment	No of Experi- ments	Left Cerebral Gray Matter	Left Cerebral White Matter	Right Cerebral Gray Matter	Right Cerebral White Matter	Cere- bellar Gray Matter	Brain Stem
1 Normal controls*	5	79.4	68.0			79.6	70.9
2 Trauma No operation*	15	79.9	68.9			79.7	71.1
3 Left hemisphere exposed No trauma*	7	79.0	68.6	79.5	68.5	79.9	70.9
4 Left hemisphere exposed Trauma*	6	79.3	67.1	79.1	66.8	79.7	70.4
5 Bilateral nephrectomy	6	79.4	66.6			79.5	71.2
6 Bilateral ureteral ligation	5	78.3	66.1			79.3	70.6
7 Ligation of superior vena cava	4	80.0	68.2			79.7	71.7
8 Ligation of superior vena cava azygos vein	4	79.9	68.6			79.9	70.7
9 Hyperthermia	4	81.1	65.7			81.2	72.5
10 Irradiation	6	79.0	65.6			79.4	70.5

* Previously reported experiments^{1,2}

SUMMARY

The water content of various portions of the brain has been determined in dogs after bilateral nephrectomy, bilateral ureteral ligation, obstruction of the superior vena cava and azygos vein, severe fever and intensive irradiation of the head

After high fever, a slight but consistent increase in the water content of the cerebral and cerebellar gray matter and of the brain stem was found. The water content of cerebral white matter was not significantly altered.

No significant alteration of the water content of the brain was found after the production of acute uremia, ligation of the superior vena cava and azygos veins, or intensive irradiation of the head.

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CEREBELLAR ABSCESES OF OTITIC ORIGIN IN NINE CHILDREN

EIGHT RECOVERIES AFTER CANNULATION

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CEREBELLAR ABSCESES in nine children have been treated surgically by the author during the past seven years. In each instance the symptoms of abscess became manifest after mastoiditis and mastoidectomy. Operative treatment was the same for all cases, and was delayed as long as possible without jeopardizing life from increased intracranial pressure, to allow the abscess wall to thicken and the acute symptoms of meningitis and cerebritis to subside. Slowing of pulse or respiration with increasing restlessness and stupor were the warning signs that surgical interference was imperative. No lumbar punctures were made, for fear of medullary herniation. Medication was avoided, especially with barbiturates or narcotic drugs which would produce added anoxic insult.

Under local anesthesia, a one-half inch trephine opening was made over the suspected cerebellar lobe with a Hudson bur, midway along a line between the occipital protuberance and the mastoid tip (Fig 1). The dura was incised one-fourth inch to allow insertion of a blunt cannula with a side opening. The cannula was inserted into the abscess allowing its contents to escape. Usually, the first pus was thin and watery and the last thick and stringy. The abscess cavity was never washed out, the wound was always closed tight with silk.

Brief abstracts of each of the nine cases of cerebellar abscess in children are appended, certain details of the cases illustrate pertinent considerations in successful diagnosis, preoperative, surgical, and postoperative treatment of this condition.

ABBREVIATED CASE REPORTS

Case 1—Judith S., age four, was admitted to hospital with painful swelling behind left ear, swelling had been discharging for two months. Child had been nervous, weak and without appetite since tonsillectomy a year before. Mastoidectomy was performed day following admission—a large quantity of pus was found and a small dural exposure was made. Extreme hyperemia of all structures made operation difficult but recovery was fairly uneventful until one month later, when child refused food, vomited, and temperature remained at 101° F for a week. Spinal fluid showed 1,575 polymorphonuclear cells, with cocci in chains. Numerous spinal taps were made during the following month. Cultures were negative.

When first seen by the author, nine weeks after mastoidectomy, the child was listless, vomiting, and showed marked ataxia of the left arm. Optic disks were rosy. Seven days later the child became comatose, there was early papilledema and considerable ataxia of left arm and leg. At operation, resistance of abscess wall was felt at depth of 3 cm, and penetration with the cannula allowed green pus to extrude. Culture *Streptococcus haemolyticus*. One ounce escaped before the child became livelier and the needle was

withdrawn to avoid traumatizing the cerebellum when the child moved. During a rapid postoperative recovery the child's papilledema disappeared within a week and the ataxia within a month. After five years of apparently normal health the child was again admitted to hospital with a stiff neck and high fever. Pneumococci were recovered from blood and spinal fluid and four days later patient expired from septicemia and meningitis.

Case 2—Margaret L., age eight, was admitted to hospital, seven weeks after an opening of both eardrums, with painful and discharging ears. After a double mastoidectomy the child continued to be drowsy, with nausea, headache and weakness of left arm.



FIG 1—Billy H. Case 9. Showing recent scar over trephine opening. Patch of adhesive marks occipital protuberance.

Right mastoid region was reopened 12 days after mastoidectomy, the dura uncovered, and the right temporal lobe needled for a suspected abscess without obtaining pus. Several spinal punctures around this time showed 50 to 100 cells, mostly lymphocytes.

Patient was first seen by the author the day following reopening of right mastoid region. Child was semicomatose, pulse 60, temperature 99.6° F. Atonia and ataxia in left arm with early choking of optic disks. At operation upon the left cerebellar lobe, 45 cc of thick greenish pus were allowed to escape from abscess whose wall was encountered at a depth of 3 cm. Pulse rose from 74, preoperatively, to 134, postoperatively, and child seemed improved. Culture *Streptococcus haemolyticus*. After 11 days of stormy convalescence the child became unconscious, cyanotic, and pulse rate dropped to 60. Twenty-five cc of glucose were administered, and patient immediately became conscious. After seven years this patient was getting along well in school and no neurologic abnormalities could be found.

Case 3—Harry C., age five, was readmitted to hospital, 15 days after a left mastoidectomy, with complaint of vomiting and headache, but did not appear acutely ill. Pulse 100, temperature normal, R B C, 3,150,000, W B C, 17,200. Spinal tap revealed clear fluid under increased pressure, with 76 cells. Culture *Staphylococcus*. Following spinal tap, the child complained of neck pain, its head was retracted and its condition became rapidly worse.

Seen by author on following day, the child was drowsy but cooperative, his pulse varied around 60, the fundi showed early choking of the disks, and there were marked

ataxia and atonia of the left arm. The neck was not rigid but the head was thrown back because of pain several times during examination (cerebellar fits). At operation, cannula was introduced directly into cerebellar lobe to a depth of 6 cm without encountering resistance. Cannula was introduced slightly upward without meeting abnormal resistance but when introduced slightly downward encountered resistance at a depth of 5 cm. On withdrawing slightly, about 2 to 3 cc of thin, flaky pus escaped.



FIG 2—Left to right Margaret L, Adolore W, Bruce R, Gloria D, Mary R, Sally L, standing on the foot on the same side as the cannulated cerebellar abscess.

The condition of the patient seemed to be somewhat improved postoperatively, but the child continued to throw its head back because of pain. On the second postoperative day breathing suddenly stopped following a spell of extreme restlessness and death followed shortly afterward.

Case 4—Adolore W, age 11. At age five patient underwent bilateral mastoidectomy following a three months' fever following scarlet fever. Admitted to hospital six years later with vomiting, severe headache and photophobia. Neck rigid. Temperature, 100.6° F. During secondary right mastoidectomy, dura and sinus were exposed and appeared healthy. A right facial paralysis was noted on reaction from anesthesia, and after operation temperature became normal, but the boy was increasingly drowsy and a right rectus palsy developed. Optic disks were elevated 2 to 3 diopters.

First seen by the author 12 days after secondary mastoidectomy, the boy was alert and cooperative but his speech was slurred. Paralysis of right sixth and seventh nerves was noted. There were marked atonia and ataxia in the right arm. Bilateral papilledema, 3 diopters. WBC, 16,250, 76 per cent polymorphonuclears. Temperature, 98.6° F. Pulse, 70. At operation, cannula inserted into center of right cerebellar lobe encountered pus at depth of 2 cm. Cannula removed after 20 cc of pus had been extruded. Culture *Streptococcus haemolyticus*. Recovery was uneventful except for a persistent slight right facial weakness, and four years later child was apparently in perfect health.

Case 5—Bruce R, age ten. After several years in which patient was troubled with right earache with discharge in the wintertime, he was admitted to hospital with headache, earache and discharging right ear. Culture *Streptococcus haemolyticus*. Child was discharged from hospital one week after right mastoidectomy and recovery

seemed normal for three weeks, after which the boy complained of headache and ran a spiking temperature. Blood culture showed no growth. W B C, 22,800, polymorphonuclears, 84 per cent. Four weeks after the mastoidectomy another mastoidectomy was performed on the same side. Temperature became normal but drowsiness increased, accompanied by headache.

When first seen by the author the boy was lethargic but cooperative, complaining of frontal headache. The neck was not rigid. There was no papilledema, although the optic disks were rosy. Coarse nystagmus on looking to the left, with the slow component to the right. Transient right facial weakness, especially noted on smiling. Ataxia on the right in the finger-to-nose and finger-to-finger tests. Atonia of the right arm. No abnormality noted in the deep and superficial reflexes. W B C, 14,500, polymorphonuclears, 95 per cent. At operation, cannula encountered resistance as of tentorium at a depth of 3 cm. Cannula reinserted slightly downward and toward mastoid tip, striking no resistance but obtaining pus at a depth of 4 cm. Ten cc of thick greenish-yellow pus allowed to extrude itself. On inserting the instrument 1 cm farther, a resistance was felt as of the bottom of the abscess cavity. When no more pus escaped, the cannula was withdrawn. Culture *Streptococcus haemolyticus*.

There was immediate improvement in the headache, but the boy continued to be drowsy. After three weeks the wound was opened and about 5 cc of pus found outside the dura. Following this the patient made a progressive and uneventful recovery. Three years after operation neurologic examination was entirely normal, the boy was getting good grades in school, was active in athletics and had no complaints of any kind.

Case 6—Gloria D, age six, was admitted to hospital with pain and swelling behind right ear after complaining for two months of recurring earache on right side. Right mastoidectomy revealed considerable pus. Culture *Streptococcus haemolyticus*. Convalescence was uneventful, but a month later the child was readmitted to hospital after ten days of headaches and fever. Child was listless, uncooperative, and weakness of right arm was noted. Papilledema, 6 diopters. Secondary mastoidectomy with needling of right temporal lobe did not reveal pus. Sulfanilamide was given but discontinued because of increasing stupor.

When first seen by the author the girl was semiconscious but cooperated enough to raise her arms. The right arm was ataxic and could not be supported voluntarily because of atonia. The grip was fair in both hands. Moderate neck rigidity. Diminished knee jerks. Marked choking of disks. W B C, 12,500. Temperature, 98.6° F. Pulse, 65. At operation, definite resistance was found at a depth of 2 cm. On pushing the cannula through this resistant tissue, yellow pus was encountered and one ounce drained. When no more pus would flow, the cannula was withdrawn. The tension on the dura was markedly decreased following this procedure. On discharge two weeks after operation there was no evidence of atonia or ataxia, although a decreasing papilledema was still present. When last seen, two years after operation, the neurologic examination was entirely negative. The child was doing well at her studies and was said to be an excellent tap dancer.

Case 7—Mary R, age seven, was admitted to hospital after six days of pain and discharge from right ear. Temperature, 101.5° F. During mastoidectomy 11 days later, pus under pressure was found. Culture *Streptococcus haemolyticus*. Temperature dropped to normal following operation but child became drowsy and vomited.

Patient was first seen by the author ten days after mastoidectomy. Right arm was ataxic. Photophobia was noted but optic disks appeared normal. At operation, abscess cavity was entered at depth of 3 cm and 10 cc of thin pus escaped. Aspiration with a 20 cc syringe produced 5 cc of thick, slimy pus before needle clogged and was withdrawn. Culture *Streptococcus haemolyticus*. Patient improved but remained irritable, vomited occasionally and showed ataxia of right arm and nystagmus. Fundi remained normal and mastoid wound healed completely.

Three months later child was again admitted to hospital because of increasing head-

ache, vomiting and atonia of right arm and leg. Examination showed bilateral choked disks of 3 to 4 diopters, right rectus palsy. The child appeared to be myxedematous. Extreme ataxia and atonia in the right arm and leg. During secondary operation very marked resistance was encountered at a depth of 5 cm with the cannula directed toward the left pupil. This was at first thought to be tentorium, but on pushing the instrument further a cavity was entered and two ounces of thick greenish-yellow pus escaped. When dropping of the pus through the cannula slowed up, aspiration with a syringe was attempted, but without obtaining more pus. Culture *Streptococcus haemolyticus*.

This child was discharged six days after operation. The irritability disappeared immediately. One month after operation the myxedematous appearance had disappeared, the optic disks were flat and only a trace of ataxia and internal strabismus remained. A year later no neurologic abnormalities could be noted and the child was getting along well in school.

Case 8—Sally L., age five, was admitted to hospital with left-side earache, vomiting and temperature of 100° F. History of bilateral headaches for over three years. The ear had been opened the day before admission and sulfanilamide was given for four days after admission. Roentgenograms showed second degree left mastoid involvement and complete left mastoidectomy was performed ten days after admission. Culture *Streptococcus haemolyticus*. Temperature continued to range from 99° to 102° F, and the girl became increasingly irritable and irrational. She was drowsy but presented no abnormal neurologic signs except neck rigidity. Spinal fluid examination showed no increase in pressure, 285 polymorphonuclears, Pandy, four plus. Spinal fluid culture, staphylococcus, atypical. Sulfanilamide was again administered and several transfusions given. Although the temperature became normal, the child grew increasingly drowsy with generalized twitchings, suggesting a tuberculous meningitis to one observer.

When first seen by the author, three weeks after mastoidectomy, she was drowsy and irritable. Early papilledema was noted and the neck was rigid. There was marked ataxia and atonia of the left arm and leg when raised by examiner, the child being entirely uncooperative. Because of the irregular pulse, ranging from 42 to 60, and the desperate appearance of the child, operation for suspected cerebellar abscess was performed immediately. On incising the dura a small amount of cerebellar cortex herniated through the small nick. A cannula was inserted and penetrated the resisting abscess wall at a depth of 2 cm. One-half ounce of yellow fluid squirted out and gentle aspiration removed another one-half ounce of thick yellow pus. Culture *Streptococcus haemolyticus*.

During the procedure the child became more rational and cooperative. Recovery was immediate and the patient was discharged five days after operation. A year later neurologic examination was entirely negative and the parents thought the child normal in every way.

Case 9—Billy H., age four. Headache, irritability and neck rigidity had been present before a right mastoidectomy. After operation the child became drowsy and developed increasing ataxia of the right arm and leg. There was little elevation of temperature at any time.

Two weeks after mastoidectomy the patient was seen by the author and a cannula was introduced into the right cerebellar lobe allowing 45 cc of pus, under marked pressure, to escape. Culture *Streptococcus haemolyticus*. Recovery was uneventful and neurologic examination seven months after operation was entirely normal (Fig 2).

Discussion—In all the cases the principal diagnostic and localizing signs were atonia and ataxia of the arm on the same side as the abscess. These signs could be observed, whether the child was cooperative, irritable or stuporous, if the arms were lifted from the bed and allowed to fall away. In addition, various symptoms of cerebral anoxia from increased intracranial pressure were found: character change, headache, irritability, vomiting, papil-

ledema and stupor. Occasionally, differential diagnosis was difficult between a brain abscess in the cerebellar lobe on the side of the atonic and ataxic extremity and in the temporal lobe on the opposite side. With the cerebellar abscess the grip in the ataxic extremity is little different from that in the other hand. With the temporal abscess, the arm is usually paretic and the grip is weaker in the hand on the side opposite the abscess.

In waiting for a cerebellar abscess to wall off, there is a perilous balance between brain infection, on the one hand, and increased intracranial pressure, on the other. Chance, as well as judgment, may play a great part in the successful outcome of any case. The value of surgery is principally in the mechanical relief of pressure, giving the brain a better chance of conquering and surviving its infection.

After the upper attachment of the suboccipital muscles is spread with a self-retaining mastoid retractor, the trephine opening is ordinarily made about one-half inch below the transverse sinus. Care must be taken that the opening is not over or above the sinus. After nicking the dura, the cannula is gently forced into the cerebellum and directed slightly toward the mastoid tip. In only one case was the abscess found to be more centrally located. The cannula should be inserted and withdrawn very slowly to allow thick pus to escape. Pressure from within is usually sufficient to empty an abscess completely because, when the pus stops dripping through the cannula, aspiration with a 20 cc syringe seldom obtains more pus. Still, it is well to use the syringe to make sure the cannula has not been plugged with fibrinous material. No irrigation of the abscess cavity is employed.

Any anoxic insult which might be added incident to treatment must be avoided. Operation should be performed under local anesthesia and narcotic or hypnotic drugs are contraindicated. In all of the cases outlined chemotherapy was discontinued as soon as the cerebritic stage was passed and before any surgical intervention was attempted.

Previous attempts had been made in two of the cases to needle a suspected temporal abscess through an infected mastoid wound. Such a practice proves the considerable immunity of the brain to infection, but is not a desirable neurosurgical procedure. Spinal puncture should not be made if a cerebellar abscess is suspected, for this procedure increases the danger of medullary herniation.

The only child in the series which died after operation was fighting not only an active staphylococcic meningitis, but also the untoward effects of a spinal tap, which made immediate operation imperative and prevented proper walling-off of the abscess. The other child, who died of pneumococcic meningitis after five years of good health following the drainage of a streptococcic abscess, is just another illustration of the variable immunity of the central nervous system to different types of organisms.

Grateful acknowledgment is made to Drs. William S. Gonne, J. Milton Robb, G. M. Laning, Seymour Ross, William G. G. Coulter, J. Gerard Campbell, Carl C. McClelland, Wesley W. Wilson, and Jacob S. Wendel, who referred these cases to the author.

THE SURGICAL TREATMENT OF INTRACRANIAL ANEURYSMS OF THE INTERNAL CAROTID ARTERY*

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INTRACRANIAL ANEURYSMS arise on any part of the arterial vascular tree. Over one-half spring from the circle of Willis, the remaining are distributed throughout the brain and from the vertebral and basilar arteries. There are three types of intracranial aneurysms: (1) Congenital, comprising about 80 per cent of the entire number, (2) arteriosclerotic (about 15 per cent), and (3) mycotic (about 5 per cent). Contrary to a very prevalent opinion, syphilis plays no rôle, or almost none, in the formation of these aneurysms. There are no surgical possibilities in the mycotic aneurysms, which are one of the terminal phases of endocarditis, and are almost always in the brain substance and on the middle cerebral artery or one of its branches. Arteriosclerotic aneurysms offer very little return from surgery, as yet none have been cured, though it is quite probable that the vertebral and basilar aneurysms may be benefited by ligation of one vertebral artery in the neck. It is principally with the congenital aneurysms that surgery has a place in treatment. Usually they are small berry-like nubbins in one of the vascular trunks—not uncommonly they are multiple. Since their walls are congenitally defective, they give rise to intracranial hemorrhage—usually the so-called subarachnoid hemorrhage—and in the early years of life, although they may rupture in later life.

Until a sudden rupture, aneurysms are usually silent. The immediate result of the hemorrhage depends in large degree upon the presence or absence of opposing tissue at the site of the rupture. If the rupture is into cerebral substance, the bleeding may be controlled, and a large progressive false aneurysmal sac will form and in time, by gradual expansion, give signs and symptoms like those of a brain tumor. Should the rupture be along a structure like the third nerve or the carotid artery itself, the bleeding may be controlled temporarily, but subsequent ruptures will probably occur and usually end fatally. Should there be no opposing tissue, the bleeding would then be into the cerebrospinal fluid (the cisternae) and rapid, fatal hemorrhage is almost inevitable.

The great deterrent to operative intervention in subarachnoid hemorrhage is the inability to localize the aneurysm by symptoms or signs. At times, there are prodromal manifestations but all too frequently the patient passes quickly into coma and then, all too frequently, there are no objective localizing signs.

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If it were even possible to localize the side (right or left) of the aneurysm, the operative exposure would be adequate to disclose the aneurysm, if it were located on the circle of Willis. This is a hope for the future, for up to the present time the only aneurysms that have been operated upon successfully are those causing a third nerve palsy or paralysis—a sign that is almost but not quite pathognomonic of an aneurysm and its location.

In a search for better and earlier means of diagnosis of aneurysms and their location, I have analyzed 103 cases that have appeared in the records of the Johns Hopkins Hospital. In a very high percentage of cases, no help was elicited, but in many of them there was adequate information to determine the side of the lesion. In nearly all of the aneurysms of the middle cerebral artery there was hemiplegia, but it is highly improbable that more than an occasional aneurysm of this vessel can ever be cured without a permanent hemiplegia, and treatment of this character would not be considered. On the other hand, some aneurysms of the anterior cerebral artery give a partial hemiplegia or Babinski, and these are amenable to treatment, although none have as yet been cured. Bilateral cerebellar and brain-stem signs of sudden onset may also indicate aneurysms of the basilar and vertebral arteries, but here again there are little prospects of a cure by surgical means, at least none have yet been successfully treated. It is the silent aneurysms, with few or no signs or symptoms arising from the internal carotid arteries and the circle of Willis, that offer the maximum room for prompt surgical treatment.

The only symptom that is useful in detecting the side of the aneurysm is an unilateral headache, or pain in one eye. This may or may not be present, either as a prodromal symptom before rupture, or as an excruciating pain at the time of rupture, and even occasionally it may be misleading. A positive

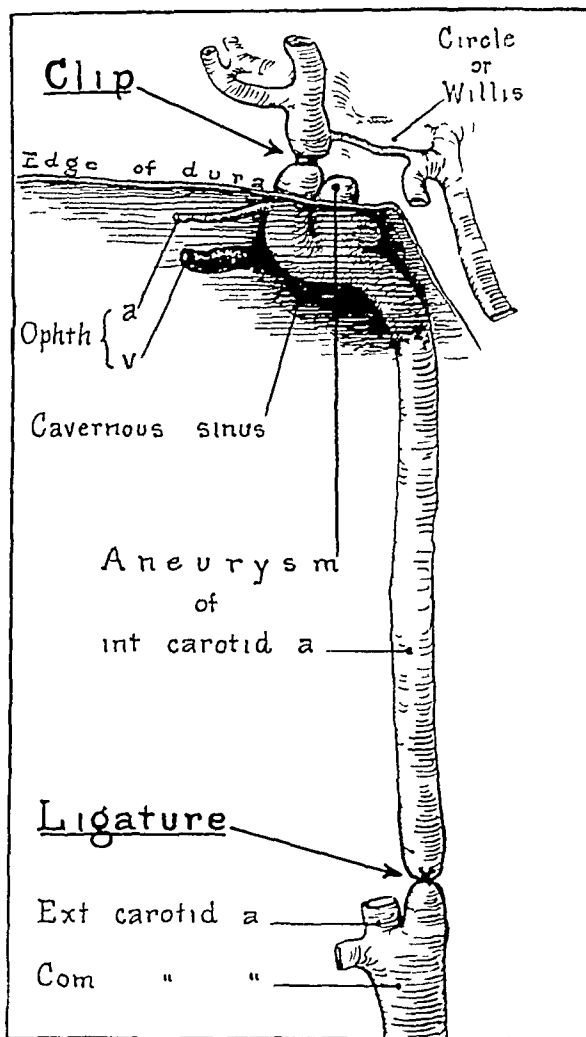


FIG 1.—Diagrammatic drawing illustrating the method of curing carotid aneurysms arising within the carotid canal. A clip is placed on the internal carotid artery intracranially, and the internal carotid artery is ligated in the neck. This traps the aneurysm between the two ligatures, and the only sizeable branch between the ligature is the ophthalmic artery. Vision is not lost as the result of the ligation.

Babinski sign may at times betray the side of the lesion, but by far the most important sign of all is weakness of a third nerve

Intra-arterial injections of thoriostat have for some time been used to define aneurysms and with remarkable results. Against its use is the risk of cerebral emboli, the frequent necessity of injecting both internal carotid arteries, since only one side fills well with one injection, and in the acute stage of bleeding the patient is much too ill. For patients who are not in the acute stage of subarachnoid bleeding, it will doubtless be a distinct asset,

but should be employed with caution and discrimination

Thirteen intracranial aneurysms of the internal carotid artery have been operated upon, all have been diagnosed and localized by a third nerve palsy or paralysis, plus sharp, severe, sudden pains in the eye and the corresponding side of the head. Six of these arose in the carotid canal and broke through into the cranial chamber alongside the internal carotid artery. Five of these are cured, the longest for four and one-half years. The single death was due to a rupture of the carotid artery in applying to a very large arteriosclerotic vessel a silver clip that was too small. This was a case of an arteriovenous aneurysm (pulsating exophthalmos). The arterial aneurysm which had ruptured and caused this arteriovenous fistula was found at necropsy. Seven arose from the internal carotid artery intracranially, before the anterior cerebral artery is given off. Five of these are cured and two have died.

Two of the five cures were obtained by placing a silver clip on the neck of the aneurysm, leaving the carotid artery intact. The re-

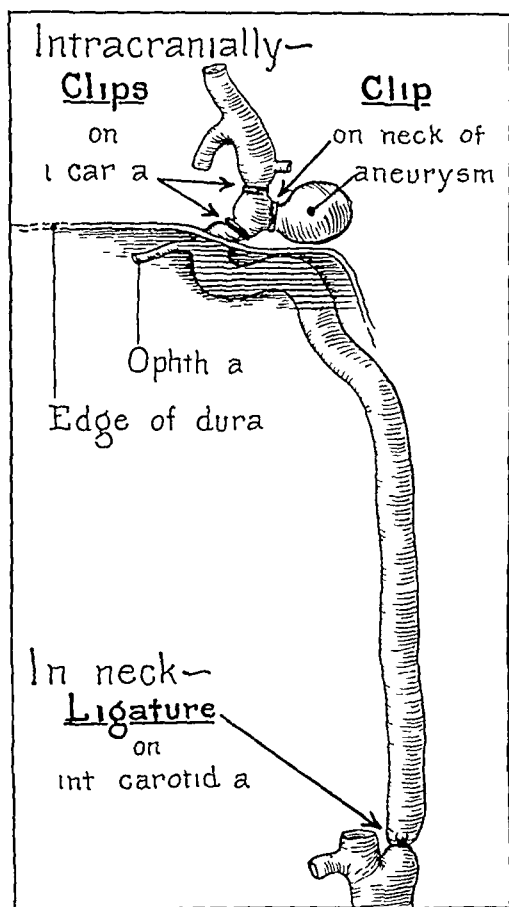


FIG 2—Diagrammatic drawing illustrating the method of treating intracranial aneurysms arising from the internal carotid artery before the first branch is given off. The neck of the aneurysm may be clipped and nothing done to the internal carotid or the internal carotid may be clipped on either side of the neck of the aneurysm, thus isolating it. The aneurysm is then shrunk by the electrocautery in order to remove its contact with the third nerve or it may actually be removed; this was done in one case.

remaining three cures were obtained by clipping or coagulating with the cautery the internal carotid artery on both sides of the aneurysm. The two deaths were due to (1) an abnormally placed posterior communicating artery, which was between the two clips and prevented collateral circulation, and (2) to subsequent rupture of the electrically coagulated internal carotid artery. This

occurred one month postoperative, after the patient had returned home, and was presumably cured. Ligation of the internal carotid artery in the neck would have prevented this death.

The mortality in this series is, therefore, 23 per cent—the cures 77 per cent.

DISCUSSION—**DR FRANCIS C. GRANT** (Philadelphia, Pa.) This question of aneurysms and their treatment is a matter of considerable interest because I think we may find that a good many of the cases that we see which have been classified as subarachnoid hemorrhage are going to turn out to be aneurysms, and may offer post-operative treatment.

The case that Doctor Dandy referred to, that was operated upon by him, in which the diagnosis of aneurysm was made by the use of thorotrast, has, in our instance at least, opened a good many possibilities. We have had two similar cases since, in which the thorotrast has been used and the aneurysm identified, and we are hoping to have the opportunity to operate upon those particular cases.

Our experience with aneurysm has not been as fortunate, so far as the operative procedure is concerned, as Doctor Dandy's has been.

During the last ten years, we have had 14 cases of aneurysm that have gone through the clinic and been identified, nine of them clinically and five pathologically. The five pathologic cases have been found in a series of, roughly, 1,100 verified brain tumors, so I presume the percentage of aneurysm to all other cases is about one-half of 1 per cent. The cases that are considered as having been verified clinically are cases similar to the ones to which Doctor Dandy referred, where there has been a paralysis of the various optical nerves, usually with hemiplegia, and on the history, and, at times, by roentgenologic and other evidence, the case has been suggestive of aneurysm, but unfortunately we have not, as I say, realized the operative possibilities in those cases which have been sent home.

The type of case that we have seen most commonly is similar to one that we had two years ago, with aneurysm of the basilar artery, a presumptive diagnosis was made of a cerebellar lesion. The patient died rather suddenly, after the administration of an enema. This lesion was found.

The other kind has been of the type where there has been a large intracerebral aneurysm, the possibilities as far as operation is concerned in those cases, of course, being very limited. But I am quite sure that most of these cases of subarachnoid hemorrhage—certainly those that show clinical and pathologic evidence of the involvement of the ocular nerves, particularly the third—should be subjected to thorotrast injection. With the injection of thorotrast, one may very well find the position of the aneurysm. As Doctor Dandy has said, if it lies on the circle of Willis, very little can be done, but if it lies along the carotid, certainly, exposure is warranted and an attempt can be made either to trap the aneurysm between the silver clips, as he suggested, or to put a silver clip on the neck of the aneurysmal sac itself, and by that means I see no particular reason why a good many of these cases should not be cured. Of course, it is not quite as easy an operative procedure as one might gather from Doctor Dandy's description, but, nevertheless, it is an operative procedure which, to my mind at least, is entirely justified, because if nothing is done these aneurysms will go on to rupture, with ultimate death of the patient.

DR GILBERT HORRAN (Boston, Mass.) This is a most important communication of Doctor Dandy's, and I am sure it interests all of us, but particularly the neurosurgeons. It has opened up a line of treatment for certain types of intracranial aneurysms, which I am sure we must all follow in the future.

We have not been fortunate enough to identify an aneurysm intracranially which we could clip or trap in the way Doctor Dandy has described. However, we have had six examples of intracranial aneurysms which we have exposed at operation and have treated in another way, a way which has been described by Mr. Jefferson, of Manchester, England, and by Mr. Dott, of Edinburgh. This method consists in packing pieces of muscle around the aneurysm and thus hope at least to prevent any further rupture. These

patients have all survived and are alive anywhere up to five or six years at the present time

One aneurysm, upon which we have not operated, was demonstrated by thorotrast, and one was identified but nothing was done to it since nothing could be accomplished, except to divide the ninth nerve, because of the pain the patient was having

It seems to me we must be a little conservative about the attitude we take in regard to operation upon aneurysms, as there have been a large number of patients passing through the clinic who have had the diagnosis of intracranial aneurysm made, because of third nerve palsy and pain over the eye of the same side. Whether they are aneurysms or not, we do not know because we have not subjected them all to thorotrast. In fact, we have only, in two instances, demonstrated the presence of aneurysm by thorotrast. The other cases have not, as a rule, shown anything roentgenologically from which a positive diagnosis could be made, so the aneurysm diagnoses have been made on symptomatology and signs, but a large number of cases with one rupture have recovered and gone on for many years in perfectly good health. Thus, it seems to me there is a chance for a good many of these aneurysms to take care of themselves, if they have only a single rupture, because very possibly when there has been subarachnoid bleeding around them a clot is formed, and, because of the organization of that clot, I believe some of the aneurysms permanently cure themselves.

It is a most interesting and valuable paper. I think we should be on the watch for those aneurysms which we can cure in this way by ligation. But if the aneurysm, as presented at operation, does not offer a chance of putting a silver clip on it, this method of putting the muscle around it, I think, is an excellent one.

CANCER OF THE LIP*

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PART II

Radiation Treatment of the Primary Lesion—Superficial cancers of the lip (1–5 Mm in thickness), whether small or covering an area of several square centimeters, are preferably treated by radiation, in our opinion, not because of a higher cure rate but because of the superiority of the cosmetic results. For lesions of greater thickness, the choice of radiation or surgery is somewhat optional and depends upon the available equipment and the skill and experience of the surgeon in the use of one or the other of these methods.

For early growths, which have not progressed much farther than keratoses, unfiltered radon is an excellent method. At Memorial Hospital such radiation is obtained by the so-called “radon bulb” which consists of a thin glass bulb about 5 Mm in diameter containing 200–500 mc of radon seeds which is held in contact with the lesion by a special holder for a few seconds or minutes, depending on the desired dose. There is no filter except the thin wall of the glass bulb. With doses of from 400 to 1,000 mc minutes (depending on the extent of the lesion), these small growths can be controlled with a minimum of discomfort and with a nearly perfect cosmetic result. This method should not be employed in lesions of greater depth than about 1 Mm. In many of these early growths a biopsy is not justified, and if no histologic proof of cancer is obtained, the cases cannot be included in a statistical report of cures of cancer of the lip—an objection of academic rather than of practical importance.

For superficial lesions, more advanced than the above but whose thickness is not greater than 2–3 Mm, there are several effective radiation methods, namely, (1) low voltage (100–140 K V) lightly filtered roentgen radiation, (2) contact application of filtered radon tubes held in dental compound mouldages, (3) interstitial radiation in the form of gold radon seeds, radon, or radium needles. Although all of these methods employed singly are efficacious, the best cosmetic results are undoubtedly obtained by low voltage roentgen radiation supplemented in some instances of thicker lesions by the implantation of small doses of interstitial radon.

In using low voltage roentgen radiation, the surface of the tumor in the lip (including an apparently healthy margin of 3–5 Mm) is exposed through

an opening in a shield of lead foil applied to the lip (Fig 6) Individually fitted shields should be made for each case, and the lesion itself so positioned that the surface of the tumor may be exposed as nearly as possible at an angle of 90° to the incident beam If the growth tends to extend on to the inner surface, a moulage of dental compound in the lower gingivolabial gutter may be used to evert the lip, so as to expose the entire growth The dosage must vary considerably, depending on the diameter of the area exposed and the quality of the roentgen radiation, as determined by the voltage and the

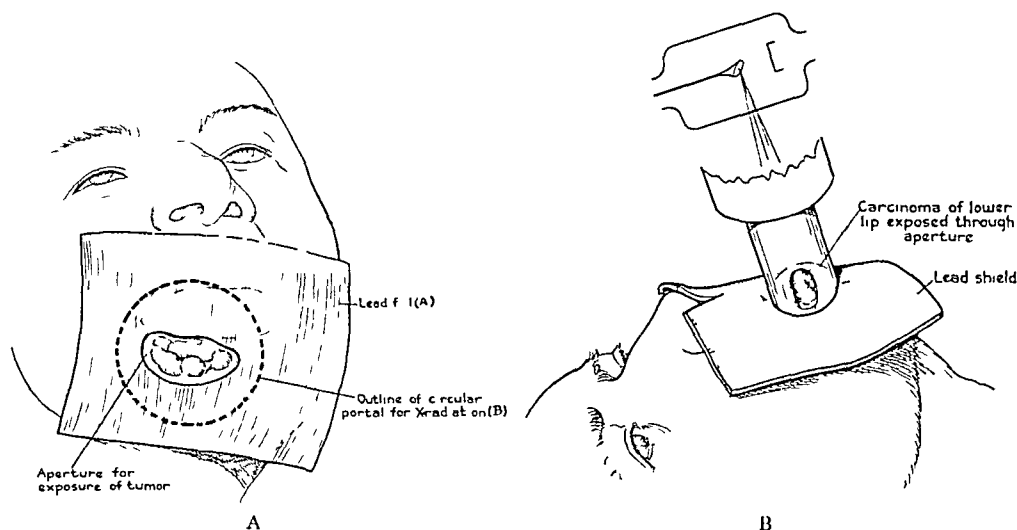


FIG 6—The treatment of cancer of the lip by low voltage roentgen radiation (A) A special shield of lead foil is used with an aperture which is large enough to expose the tumor and a margin of 3–5 Mm (B) The cone which limits the beam of the roentgen rays is then carefully centered over this aperture

filter It has been found, in our clinic, that in such superficial roentgenotherapy, the necessary dosage as expressed in r may be made to vary more than 100 per cent by changing one or more factors as, for instance, by dropping the voltage from 140 to 100 K V, by varying the filter from 1–3 Mm Al, or by dividing the treatment into fractions over a period of five to 15 days instead of giving the entire exposure at one sitting Since there are so many variable factors, it is difficult to give complete or specific dose recommendations for this type of therapy In general, for areas about 1 cm in diameter, the required dosage ranges from 9,000–15,000 r, depending upon the exact physical factors of the roentgen ray machine, and whether the irradiation is administered all at one time or in fractions over longer periods (five to 15 days) In lesions of 4–5 Mm thickness, the advisability of supplementary irradiation by a small dose of radon seeds inserted under the base of the growth should always be considered The individual strengths of the radon seeds for such supplementary treatment should not exceed 1–1.5 mc each Not more than two or three seeds should be used in the average case, and they should always be placed at a depth of at least 5 Mm below the surface of the vermilion border so as to minimize the danger of surface necrosis

Contact irradiation by filtered radon tubes is also an excellent method, although it has the disadvantage of producing more late radiation sclerosis and atrophy than soft roentgen radiation. In recent years, this method has

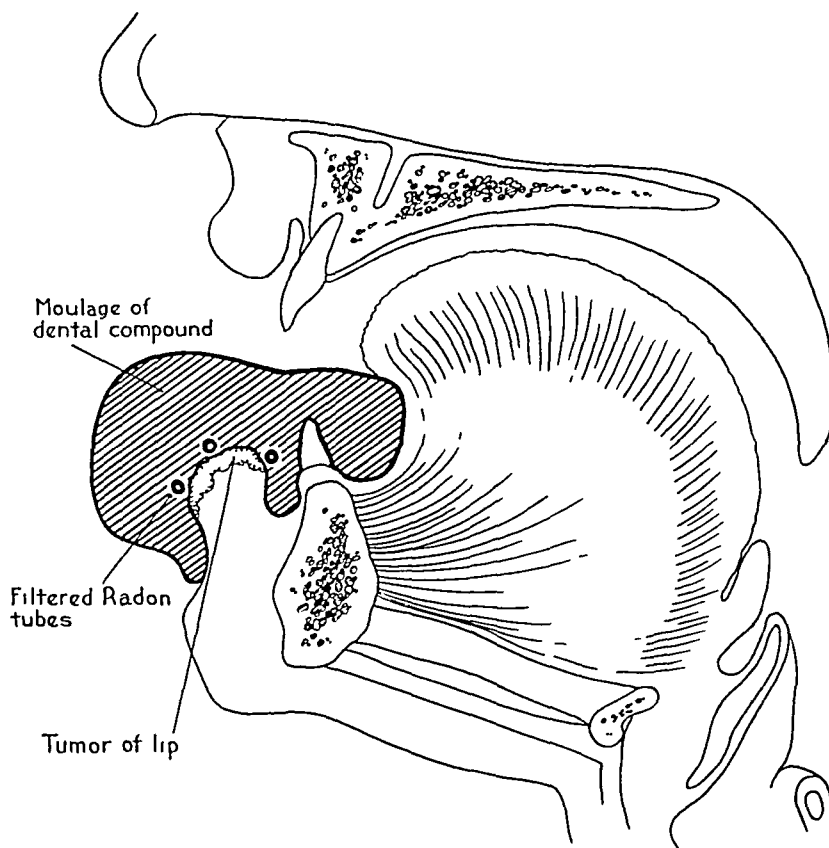


FIG 7A

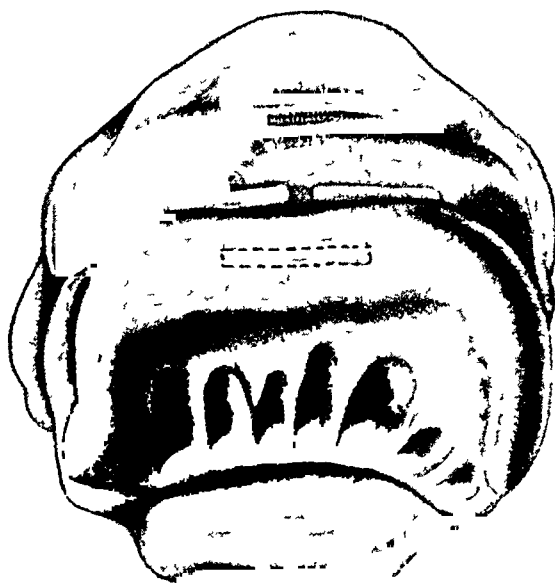


FIG 7B

FIG 7—A and B Dental compound moulage to hold filtered radon in contact with lower lip for treatment of superficial lesions

been replaced almost entirely at the Memorial Hospital by low voltage roentgen radiation for lip cancer. In the technic of contact irradiation devised by Janeway,²⁶ the filtered radon tubes are held in contact with the lower lip in a mouldage of dental compound (Fig 7 A) which is made as follows. About one and one-half squares of ordinary dental modeling compound are heated to a soft plastic consistency and molded about the lower lip. Some of the compound is forced down into the gingivolabial gutter and also between the teeth, in such a manner as to hold the lip, the growth, and the radiating sources away from the lower alveolar ridge. The patient is instructed to bite into, *but not through*, the portion of the compound which has been forced between the teeth. While the compound is still warm and plastic, it is carefully molded about the lip and the growth so as to cause a minimum distortion of these parts (Fig 7 B). If the patient is seated in front of a wash bowl and a rubber tube is connected with the cold water faucet, the mouldage may be rapidly cooled and hardened before removal.

The mouldage, when removed, should present an accurate impression of the lower lip and a visible imprint of the lesion. There should be a ridge of the compound 6-7 Mm thick between the inner surface of the lip and the alveolar ridge, and, also, the undistorted imprints of the teeth so that the applicator can be replaced exactly in its original position. If the patient wears dental plates, these are left in place when the impression is taken. The plates will come out embedded in the mold when the latter is removed and will serve, as well as the natural teeth, to hold the applicator in its correct position.

When the mouldage is removed, the portion which represents the lower lip should show a definite imprint of the lesion. Holding the mouldage next to the patient's lip, and guided by inspection of the growth, an outline is scratched (or otherwise marked) so as to encircle the imprint of the lesion by a margin of at least 5-6 Mm. The applicator is then ready for the placement of the radon tubes. The platinum radon tubes, as used in our clinic, are 1.6 cm in length with a wall thickness of 0.5 Mm of platinum, and they contain glass tubes of radon. Their individual strengths may vary from 25 to 75 mc each. If a number of short radium element needles are available, they may be substituted for the radon tubes just described. With a hot metal die of the same size as the radon tubes, grooves are made within the outlined area so that the tubes, when placed, will lie from 4-6 Mm apart and about 1-2 Mm below the surface of the mold. Their position is so arranged that they are distributed as evenly as possible over the surface of the lesion to produce a maximum of cross-firing. The tubes are sealed in place by melted paraffin. The area to be irradiated (that inscribed by the scratch mark surrounding the lesion) is then calculated in square centimeters.

The applicator is now ready for use. It is carefully replaced exactly in the position in which it was made, care being taken that the teeth or gums fit accurately into their original positions. The patient is instructed to force his lower lip up firmly into the groove into contact with the radon tubes.

In order to protect the upper lip from unnecessary radiation, a small piece of lead may be placed between it and the upper surface of the moulage, or a roll of gauze will hold the upper lip away and protect it by distance.

The dosage is calculated in millicurie hours per square centimeter of area treated, and it should be emphasized at this point that the figures given below are correct only for the filter specified, that is 0.5 Mm of platinum. If the area is small (up to about 3 sq cm), a dose of about 85–90 mc hrs per sq cm is given. The minimum total dose ever given with this applicator should be at least 240 mc hrs with three tubes. Moderately thicker lesions should receive higher doses per square centimeter. If the area to be treated is 5–6 sq cm or more, the dose should be decreased to 70–80 mc hrs per sq cm (350–500 mc hrs total), because of the cross-firing from the several tubes. In any case, it is best to err moderately on the side of heavy rather than light dosage, since delayed healing is preferable to recurrence. As with unfiltered roentgen radiation, lesions over 4–5 Mm in thickness should, ordinarily, have supplementary interstitial radon in the form of one or more weak gold seeds implanted under the base of the lesion. The interstitial use of radon seeds or radium needles alone, as advocated by some authors, is not suitable for lip cancer because of the high incidence of radionecrosis if the doses are adequate.

Operation may be refused in certain cases of bulky tumors of the lip which, as a general rule, are best treated by surgery. If the patient will not submit to surgery, radiation is the only other possible method of treatment, and adequate dosage necessitates the use of interstitial irradiation with seeds or needles at least as a supplement to external irradiation. The dosage in such cases must be calculated in the same manner as for bulky tumors elsewhere, with a tissue dose of 8–10 SED (skin erythema doses) given into the tumor. The method of calculating tissue doses of radon seeds for tumors of various sizes is given in Table II. Although the treatment of these bulky lesions of the lip with massive doses of interstitial radiation in the form of seeds or needles is invariably complicated by a rather long period of healing, excellent results are often obtained.

Surgical Treatment of the Primary Lesion—Although from the cosmetic standpoint radiation methods are almost always superior to surgical excision for small lesions of the lip, it must be admitted that the wedge-shaped excision for small tumors will offer an equally good chance of cure *provided that a safe margin is allowed*. Except in the determination of this safe margin (5–7 Mm), these operations are not difficult, and in some surgical clinics are performed in the Out-Patient Department. No particular description of technic will be attempted in this report except to state that the careful approximation by sutures of both the skin and mucous membrane edges is essential for the best cosmetic results.

Cheiloplasty—In the more advanced, deeply infiltrating and eroding lesions 2 cm or more in diameter (which make up over one-third of our total group), surgical excision and plastic closure is undoubtedly the preferable

method In such cases, the simple V-shaped excision is usually inadequate To be safe, the margin of the excision in these lesions must be wider (1 cm or more) than in early cases, the operative defects are, therefore, rather extensive, and the closure complicated The details of the technic of plastic repair of these operative defects are of considerable importance in obtaining the best cosmetic and functional results

These advanced lesions are often 5-6 cm in diameter, or even larger, and may invade the entire vertical diameter of the lip and extend into the skin and subcutaneous tissue over the chin or laterally past the labial commissures into the substance of the cheeks or upper lip In other cases, the growths may fungate from the surface so as to form bulky tumors without much infiltration, of such weight as to produce marked ectropion of the lower lip These bulky noninfiltrating and fungating tumors are usually not of the most malignant variety and are commonly found without evidence of cervical metastases even after two to three years' duration From the standpoint of cure, the large size of a lesion is less important than the presence of metastases or invasion by the primary lesion of the gingivolabial gutters and jaws Provided that the primary growth can be removed with a safe margin of normal tissue, even the largest defects can be repaired by some form of plastic procedure, either primary or delayed Even though the operative defect may be difficult to close, there should be no compromise to the removal of a safely wide margin of normal tissue

There is probably no single type of operation for which more allegedly different technics have been described As far back as 1859, von Bruns⁶¹ had reviewed the literature, and classified 32 operations by 52 authors, and several times that number have been subsequently published Most of these are merely repetitions of the older technics with slight modifications, although the later authors often claim credit for their invention From the standpoint of pure mechanics, a study of this material will reveal that many of the technics are highly impractical or unnecessarily complicated We believe that the whole subject can be reduced to a few essential principles which permit of an almost infinite number of modifications, these principles are (a) The use of sliding lateral cheek flaps based upon the principles of Burow⁵¹ and Bernard⁸, (b) pedicle flaps brought down from the upper (or opposite) lip (Estlander¹⁹), and (c) tubed pedicle-flaps brought from the neck or anterior chest wall, as introduced by Filatoff²¹ The detailed basic technic for such operations has already been published by one of us³⁷ A number of the most useful procedures for this purpose are shown diagrammatically in Figures 8 and 9 As previously mentioned,^{16 20 22 42 50} the possible variations are almost infinite in number, and it is perfectly natural that the individual surgeon should introduce his own, provided that he makes no undue claims to originality

The most satisfactory anesthetic for these operations is conduction anesthesia by novocain injection of the third divisions of the fifth cranial and of both infra-orbital nerves For the incisions which extend below the lower

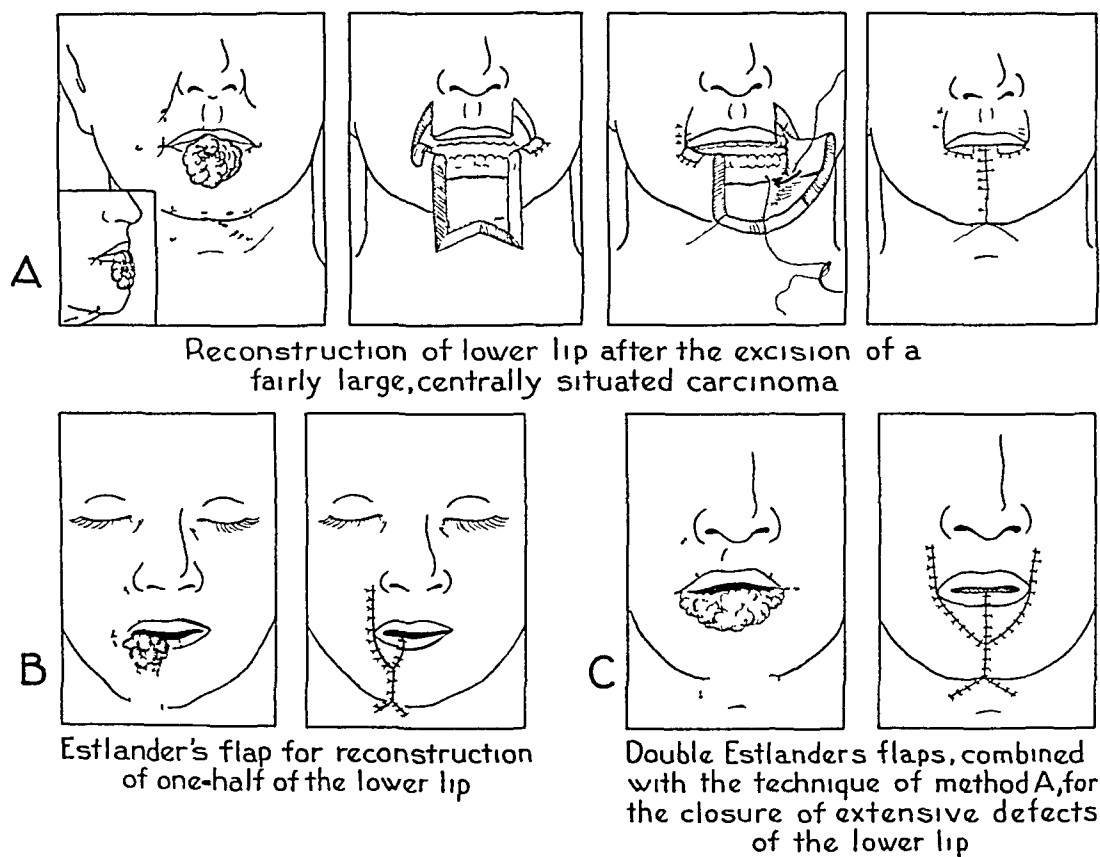


FIG 8.—Useful basic methods for cheiloplasty

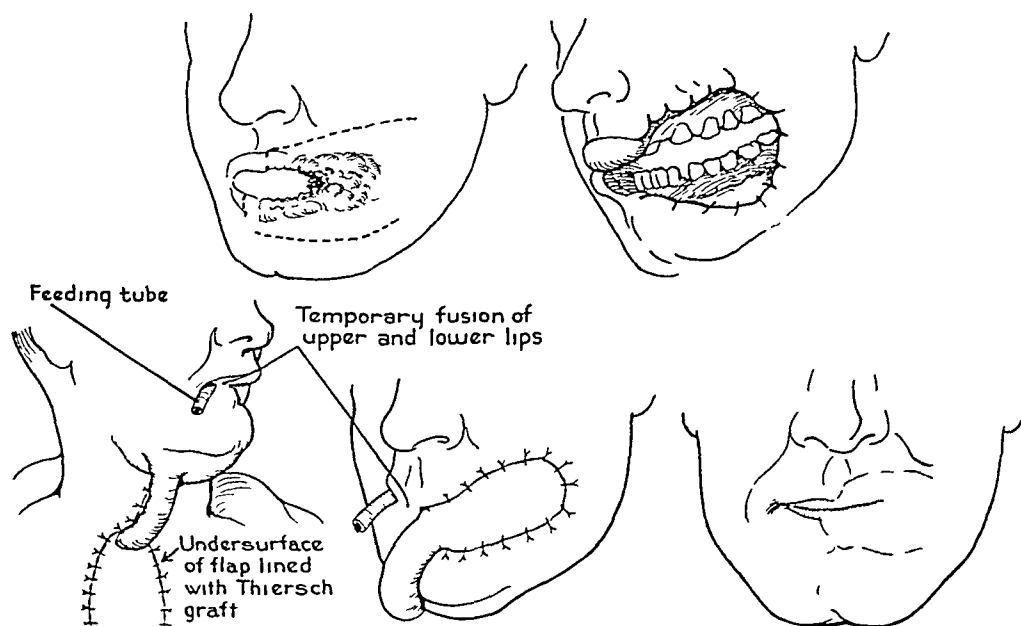


FIG 9.—Variations in technic for the closure of large lip and cheek defects by the use of migrating tubed pedicle flaps

borders of the mandible, local infiltration must be added. By using conduction anesthesia, one eliminates most of the postoperative complications of a general anesthetic, and the patient is able to expel blood or clots from the oral cavity, thereby avoiding their aspiration into the trachea. Under a local anesthetic, the patient is also able to follow directions and to open or close the mouth, as necessitated by the various steps of the procedure.

In our experience, the plastic reconstruction of all or a part of a new lower lip is always best accomplished by the use of full-thickness flaps of the cheeks or of the upper lip, except in those cases where the defect is so extensive, by reason of removal of a portion of the cheek as well, that a transplant lined by a thick split or a Wolfe graft and nourished by a tubed-pedicle is constructed from the skin and subcutaneous tissue of the anterior chest wall or neck (Fig 9). Operations utilizing unlined flaps of skin and subcutaneous tissue brought up from the neck or down from the scalp are of little practical value, since the raw surface within the mouth must heal by scarring and contracture, so distorting and shrinking the transplant as to result in both functional and cosmetic failure.

The most suitable source of tissue for the closure of lower lip defects is a lateral cheek flap from each side, which should be mobilized and drawn forward as far as possible, the closure being completed if necessary by flaps from the upper lip. In elderly subjects, the tissues of the cheeks will usually be found loose and relaxed, so that lateral cheek flaps may be advanced to close a defect 6-7 cm in its lateral diameter. These flaps should always be drawn forward in a horizontal plane which is possible only if their lower edges are outlined by incisions made almost directly backward in the sagittal plane from the lower edge of the mandible into the submaxillary regions* (Fig 8).

For moderate-sized lesions, Daland¹⁶ forms rather narrow cheek flaps by lateral incisions placed well above the point of the chin, leaving an unnecessary amount of scarring in a prominently exposed position. In any case, such technic is suitable only to moderate-sized lesions, which could probably be more satisfactorily treated by radiation or by simple V-shaped excision. In larger lesions, if the lower borders of the lateral cheek flaps are formed by incisions running vertically downward into the submaxillary regions, even the defects left after excising the larger growths may be closed with only one prominently visible scar running downward from the vermilion border in the midline over the point of the chin, the remaining portions of the scar being rather inconspicuous below the edge of the mandible in the submental and submaxillary regions.

Another point in the forming of wide lateral cheek flaps, as illustrated

* Many text-books show the lower edge of such flaps outlined by incisions parallel to the lower border of the mandible, which is inclined obliquely upward and back. Flaps so outlined will be formed on the bias, so that they must be pulled not only obliquely forward but *also downward* in order to meet in the midline over the chin. This oblique tension will cause the newly formed lower lip to be pulled upward where it will eventually come to lie unnaturally under the upper lip.

in Figure 8 A, is to detach the soft tissues from the outer surfaces of the mandibles by sharp dissection and further posteriorly by subperiosteal dissection, freeing the masseter muscles from their attachments if necessary, preserving the integrity of the facial arteries. Within the mouth, the cheek flaps are mobilized by incisions in the lower gingivobuccal gutters which, if required, may extend posteriorly upward along the anterior edges of the ascending ramus of the jaws. If lateral cheek flaps do not provide sufficient tissue for the complete closure of the defect, a satisfactory source of additional tissue is one Estlander flap (or sometimes two) from the upper lip (Fig 8 B-C). The pedicle of such a flap may be cut down to a very narrow diameter (5 Mm) provided that one preserves, intact, the superior labial (superior coronary) artery which runs very near the vermilion border. The fold of the pedicle then forms the new commissure of the mouth. Occasionally, in the excision of a moderate-sized lesion near the commissure, the defect may be completely closed by the use of one Estlander flap alone without mobilization of lateral cheek flaps.

If the defect is closed entirely by lateral cheek flaps, it will usually be found that the new lower lip is shorter than the upper lip, resulting in a "fish-mouth" deformity. This deformity may be overcome by excising Bernard³ triangles from the cheeks and upper lip lateral to the commissure, as illustrated in Figure 8 A. The mucous membrane of these triangles is left attached at the base and sutured forward so as to form a part of the new vermilion border. This modification (Bernard) serves to set the labial commissures laterally and overcomes the redundancy of the upper lip while increasing the length of the lower. The tissues of the lips and cheeks possess a remarkable degree of elasticity and flexibility, and, therefore, the edges of the defect and the flaps may be molded and adjusted to an extent not possible in most other portions of the anatomy. Furthermore, the circulation of the tissues in this region is such that with a reasonable degree of care the nutrition of the flaps need cause no concern.

During the mobilization of extensive flaps from both sides, a large operative wound will necessarily be exposed to contamination and infection from oral secretions. Much of the contamination can be avoided if, in sponging the wound, care be taken that the oral secretions are not rubbed into the exposed raw surface. Constant suction should be maintained by an assistant so as to remove the saliva before it can run over on to the wound. As soon as the mucous membrane closure has been completed, the operative field should be repeatedly washed and irrigated with Dakin's solution while the external wound is being closed.

In suturing the edges, accurate approximation of both the skin and the mucous membrane is of utmost importance. This is particularly true of all suture lines within the mouth. Either the so-called dermal sutures or silk in two layers, one to the mucous membrane and one to the skin, makes a satisfactory closure. The mucous membrane closure is begun posteriorly in the gingivobuccal gutters, the first stitch being placed entirely on the gingival

side at the posterior limit of the incision. Subsequent sutures are placed about 0.5 cm more anteriorly on the gingival than on the buccal side, and as each is tied, the mucosa is stretched more and more anteriorly so that eventually the tip of the flap will reach the midline. With reasonable care in suturing, the forward tension holds these flaps in such close approximation to the mandible that healing is usually by primary union. If the external wound edges can be drawn together firmly, there is seldom need for additional tension sutures even though the tissues appear to be very tightly stretched, since, after 24 hours, the flaps, which at first appeared to be under great tension, will have adjusted themselves so that there is no danger of separation. Healing of the skin should take place by primary union, so that the skin sutures can be removed a few at a time on the third, fourth, and fifth postoperative days. Those on the mucous surface may be left for a week or longer until the wound has healed firmly enough to permit wide opening of the mouth. Although the flaps may be very firmly applied to the outer surface of the mandible, some dead space usually persists in the wound in the submental and submaxillary regions. Adequate drainage by rubber tubes should be provided for irrigation by Dakin's solution for the first two or three days.

Wide excision with delayed closure may be indicated in certain cases. Long-standing cancer of the lip sometimes appears to be incapable of metastasizing, so that despite the rather discouraging appearance of a bulky, infected, widespread growth of the lip, there is no palpable evidence of cervical metastasis, which is the deciding factor in the selection of treatment in these cases. It is often found that such bulky lesions are movable over the mandible and that the involved portions of the lip and cheek may be completely removed resulting in a large defect which may have to be left for delayed closure.

When no immediate closure of the defect is contemplated, the removal of a bulky infected lip cancer is usually best accomplished by a thin-bladed, actual cautery under general anesthesia. The red-hot cautery blade should be moved rapidly so as to control the capillary oozing without too much charring of the wound edges. Healing of the borders is hastened if the skin and mucous membrane edges are loosely approximated by interrupted sutures. After the border has healed, contraction results in a marked decrease in the size of the defect (Fig 9), so that the later closure is facilitated. The most suitable form of plastic repair in such a case is a tubed pedicle-flap from the skin of the anterior chest wall or neck. If such a tube is taken from the neck, the necessity for at least one shift is obviated, but the cosmetic result is better if the entire tube is constructed from the chest wall, thereby eliminating all scarring of the neck. If its diameter is generous, such a tube, without any specially prepared transplant at its end, may be used alone to close fairly large defects (Fig 10). In such instances, the tube is doubled or folded upon itself one or more times, in stages, across the defect. In other cases, at one end of a pedicle-tube a transplant can be raised from the chest wall and its inner surface lined with a thick split or

full-thickness graft from the thigh or inner surface of the upper arm. A transplant so prepared may be 6-7 cm in diameter, and is indicated particularly when the defect involves the cheek. The possible variations in the form of such pedicle-flaps and in the detailed technics are almost infinite. We have

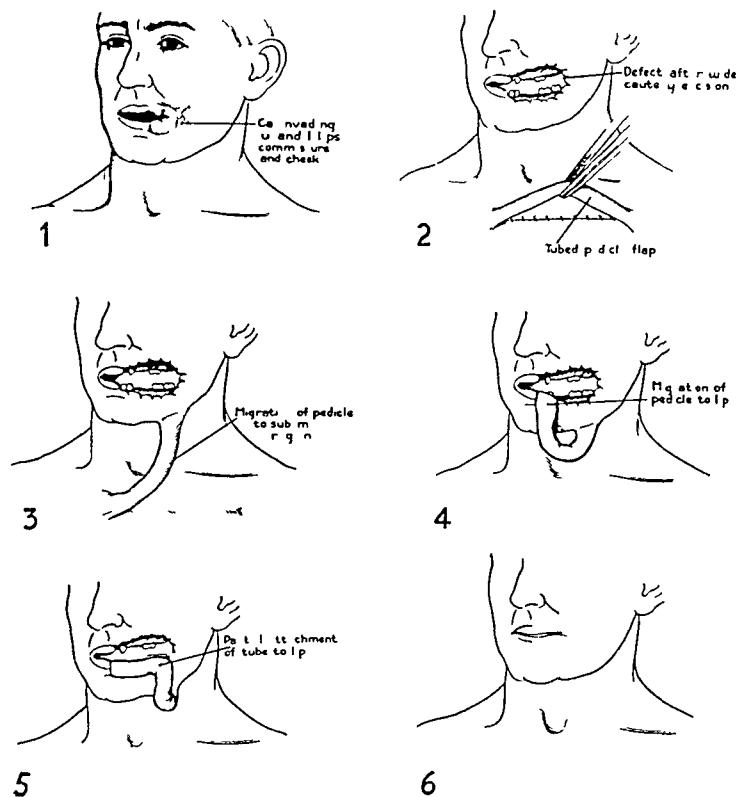


FIG 10—Alternate method for closure of large lip and cheek defects using a folded tubed pedicle without a specially prepared transplant

successfully treated advanced, complicated lip cancer in this manner, in the presence of fixed inoperable submaxillary nodes, the latter being treated by a combination of fractionated roentgen radiation and radon seeds.

Occasionally, one may be justified in combining a limited dissection of the submental and one submaxillary triangle with a plastic operation of not too great extent. It is impractical and unsafe, however, to attempt an extensive or complete neck dissection at the same time as these large cheiloplasties. Neck dissection is unsuitable even following the healing of these cheiloplasties, since there is usually considerable scarring in the upper neck following the operation upon the lip. These large cheiloplasties find their greatest field of usefulness in cases of bulky primary lesions without cervical metastases.

General Principles in the Treatment of Metastases from Cancer of the Lip—In any form of intra-oral cancer, the treatment of cervical metastasis is best considered as a problem entirely separate from that of the primary lesion. From the practical standpoint, the subject may be considered under two headings: (1) The prophylactic treatment, or that which is given in the

absence of palpably demonstrable cervical metastases, and (2) the curative treatment of clinically positive metastatic nodes. It should be realized at the outset that the opinions which we express here concerning cervical metastasis in lip cancer do not necessarily apply to cervical metastatic nodes from intra-oral cancer in general. Metastases from lip cancer are more favorable from the standpoint of treatment and differ in many other respects from those in cancer of the tongue or of the nasopharynx.

Prophylactic Treatment for Cervical Metastases—The term prophylaxis as used here refers to any treatment applied to the neck in the absence of clinically positive cervical nodes for the purpose of preventing the later development of metastases. To be exact, there is probably no method of prophylaxis against metastasis in any form of cancer except the early and successful eradication of the primary lesion. Once metastatic emboli have left the primary lesion and settled in lymph nodes, any treatment is curative rather than preventive. According to common usage, however, any treatment given before metastases are clinically evident, is termed prophylactic. At the Memorial Hospital it has been the policy for the last seven years to give no prophylactic treatment of any kind to the neck in intra-oral cancer if there is no clinical evidence of cervical metastases. The patients are re-examined at regular intervals, and only if actual metastases become clinically demonstrable is treatment given, and then with curative intent. The soundness of such a conservative plan of management should be judged on the basis of statistical analysis of the clinical behavior and the end-results in a series of observed cases as well as upon a theoretic evaluation of the merits of both radiation and surgery as related to this problem.

A survey of the literature reveals a wide divergence of opinion as to the proper methods of treatment for cervical metastasis. Some years ago, Pfluger⁴⁴ attempted to ascertain the prevailing opinion on this subject. He sent out questionnaires to representative surgeons, radiologists and dermatologists, and while the replies are interesting, the perspicacious observer will note that the opinions were undoubtedly conditioned by the specialties of the men who were questioned, that is, the surgeons, as a group, favored neck dissection, and the dermatologists favored nonsurgical methods. Radiation as a primary treatment was preferred by a few radiologists, and practically all of the radiologists advised postoperative radiation. As regards other published reports, few of the opinions expressed are based upon statistical analyses of observed clinical material and the end-results in unselected groups of cases. Some nonsurgical radiologists^{2 28 43 64} advise prophylactic irradiation in the absence of demonstrable metastases. Many surgeons^{5 20 30} advise routine prophylactic neck dissection. Some^{54, 62} believe that neck dissection alone is of value in the treatment of actual metastases, and there are those^{17 22 30} who, in the face of rapidly accumulating evidence during the past ten years, sturdily maintain that metastatic cervical cancer has never been cured by radiation alone. It must be admitted that many of the old claims for radiologic cures of metastatic cervical nodes

were not well authenticated, since there was no histologic proof of the character of these nodes. In recent years, aspiration biopsy³⁷ has provided a means of obtaining tissue for histologic examination without surgical excision. While not all surgeons and pathologists accept the validity of this technical procedure, such a reactionary attitude is rapidly disappearing. At the Memorial Hospital, the accuracy of aspiration biopsy has been checked by subsequent excision of tumors in several thousand cases and, therefore, is no longer questioned.

An analysis of several hundred cases of cancer of the lip at the Memorial Hospital has shown that, despite the size of the primary lesion, of those patients admitted without palpable evidence of cervical metastasis and in whom the primary lesion was subsequently cured, only 8 per cent developed metastases during an observation period of five years. So-called prophylactic neck dissections, therefore, could not have had even theoretic value in 92 per cent of these cases, whereas under the higher reported mortality rates³⁰ following neck dissection about 11 per cent would have died of postoperative complications. The procedure would then have killed a greater percentage (11 per cent) than it could possibly cure (8 per cent). Even under the lower reported mortality rates (3-5 per cent), the risk would, obviously, still be unjustified since the postoperative deaths approach 50 per cent of the number (8 per cent) who could expect to benefit by the procedure. If no prophylactic neck dissections were performed, over 90 operations would be avoided in every 100 cases, and in the 8 per cent which later developed clinically demonstrable metastases, neck dissection would still give a very high, if not an equal, individual chance of cure. Under such considerations, what reasonable person, either lay or medical, would choose to undergo prophylactic neck dissection in lip cancer? The validity of these figures receives striking support from the observations of Taylor and Nathanson³⁸ who report that 247 patients with lip cancer without "palpable" lymph nodes were treated by excision of the primary lesion alone, with no primary treatment to the neck. Later, neck dissection was carried out in 25 cases because of the development of "palpable" nodes and the nodes proved to be histologically positive in 20 of these (8 per cent of the total group). Richards⁴⁸ reports an even lower occurrence of subsequent metastases in cases without "palpable" lymph nodes on admission (three out of 244, about 1 per cent).

Even the ardent proponents of prophylactic neck dissection, apparently, do not practice it as routine, but modify the rigid theoretic indications by the somewhat arbitrary grouping of cases according to the size of the primary lesion or the "palpability" of cervical nodes. In any case, the percentage of histologically positive nodes in routine neck dissections is small. Kennedy³⁰ reports a collected series of 193 neck dissections in which 46 (24 per cent) were histologically positive. Figi,²⁰ in 549 prophylactic operations, found metastatic nodes in only 91 (16.5 per cent). In the latter series the philosophically minded reader will be impressed by the waste of time and effort in the 458 cases in which the nodes were found to be negative for cancer.

He is bound to doubt whether the practice of neck dissection based upon such indications is reasonable, and to wonder whether or not more could have been accomplished in these cases, if an equal amount of time and money had been spent in treating cancer only where it was demonstrably present, and in palliating the suffering of other incurable cancer patients

The contention of some surgeons that prophylactic neck dissections should be performed because of the impossibility of adequate follow-up is, in our opinion, a confession of indolence or of lack of organization. It must be admitted that, even after repeated efforts, not all cancer patients can be persuaded to return for systematic observation, but if the patient with lip cancer is negligent in this regard, the risk of recurrence is not entirely overcome by such prophylactic treatment, since the disease may recur in the neck even after neck dissection or in the lip itself. At the Memorial Hospital, only a small number of lip cases are lost to follow-up during the first two or three years, when the danger is greatest. Even up to five years the number of those traced reaches 95 per cent.

In the case of radiation, prophylactic treatment to the neck as ordinarily given does not carry with it any mortality, but if it cannot be demonstrated that such prophylactic irradiation is beneficial, then it must be conceded, at least, that it is wasteful from the economic standpoint even though otherwise harmless. As ordinarily advised and given, prophylactic irradiation in lip cancer consists of one to two SED (skin erythema doses) to both sides of the neck. Bergendal² administers only $2/3$ SED. Since such small dosage has never been observed—or at least reported—to sterilize a proven focus of epidermoid carcinoma, why should it be assumed capable of sterilizing an impalpable focus of cancer (the actual existence of which cannot be proved) simply because the patient survives and does not subsequently develop metastases? The same basic reasoning may be applied against the logic of pre- or postoperative radiation (if used in such doses). In the absence of palpable metastases, the administration of cancer lethal doses (six to eight SED) for prophylactic purposes to the entire lymph node bearing area of the neck has the same objections as prophylactic neck dissection, that is, we believe it to be entirely unjustified both from the standpoints of the deleterious local and constitutional effects and of the time and expense involved. Those who successfully apply radiation in the treatment of proven cervical metastases will readily concede that such treatment is unwarranted except when necessitated by demonstrable metastatic cancer.

Choice of Treatment Methods for Clinically Positive Cervical Metastases in Lip Cancer—The selection of the particular form of treatment for metastases in lip cancer should be based upon the clinical features of a given case rather than any partisan preference for one or the other method. If the surgeon is also a radiologist, he is likely to take a broad view and to recognize that either radiation or surgery may possess unique advantages in individual cases and that often a combination of the two is superior to either employed alone. When adequate radiation facilities are at hand, it must be realized

that in the treatment of cancer the term "inoperable" is not synonymous with "incurable"

Radiation therapy does not find so wide an application in cervical metastases from lip cancer as it does in metastases from the more anaplastic, rapidly growing tumors of the tongue, extrinsic larynx, and nasopharynx. In lip cancer, the indications for radiation, rather than surgery, are about the same as in the general group of cervical nodes and include practically all inoperable nodes and those cases in which neck dissection would be difficult, dangerous, or of doubtful value because of the age and general condition of the patient. Adequate radiation therapy of metastatic cervical nodes has certain disadvantages, among them the fact that the immediate result is not so definite and that the method is more time-consuming than neck dissection. Radiation therapy must frequently be supplemented by surgery when the bulk or mass of metastatic cancer would necessitate dangerously large dosage, if treated by radiation alone. Among its advantages is the fact that when metastases are present on admission, radiation therapy may be administered without particular risk at the same time and in conjunction with irradiation of the primary lesion.

Depending on the individual case, either radiation or surgery may possess unique advantages. Despite recently published statements to the contrary, it must now be admitted that proven cervical metastatic nodes can be cured by radiation alone. Even in certain operable cases we have found this form of treatment superior to neck dissection. In the present series of lip cancer, 11 cases of histologically proven cervical metastases treated by radiation alone have survived five years. If the question should arise as to the percentage of cures obtained by the radiation treatment of cervical metastatic cancer, we wish to point out that it would be unfair to compare the end-results of radiation with those of surgical treatment, since all inoperable, recurrent, and advanced metastatic nodes receive radiation treatment for at least palliative purposes, whereas only the early and operable cases are treated by neck dissection. In the present series, 41 neck dissections were performed with one postoperative death (2.4 per cent). The excised tissues were positive, histologically, in 35 patients (85 per cent), of whom 13 (about 31 per cent) survived five years without recurrence.

In the final analysis, it is only fair to state that in the majority of cases of metastatic lip cancer, the selection of either radiation or surgery is optional. Neck dissection is probably more expedient when uncomplicated operable metastases occur at an interval after control of the primary lesion. When complicated metastases are present on admission, radiation or a combination of radiation and surgery is preferable to neck dissection. The general condition of the patient is occasionally the determining factor in the choice of treatment methods.

Neck Dissection—A detailed description of the technic of neck dissection is beyond the scope of this paper. There are several principles of this

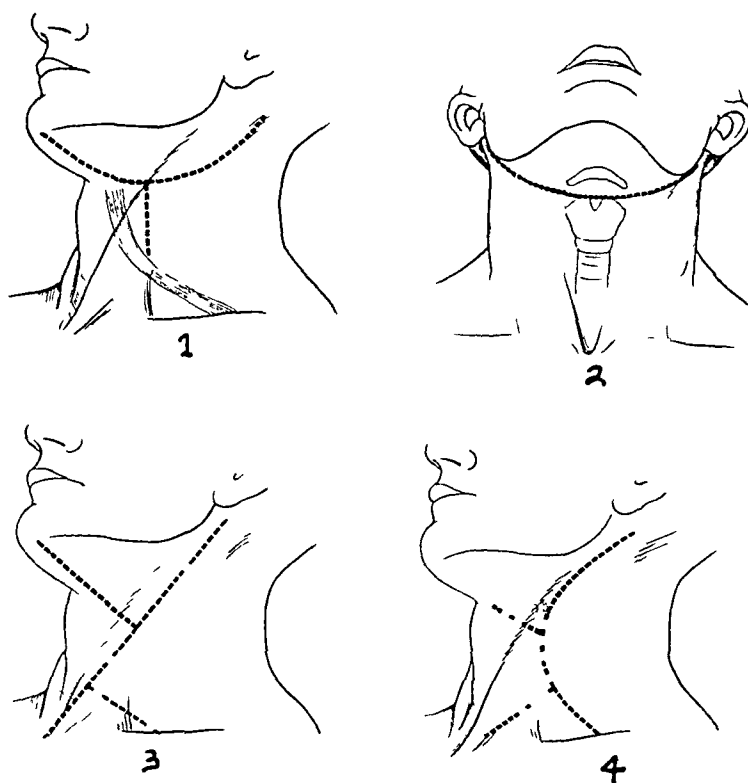


FIG 11—Useful forms of incision for neck dissection (1) For supra omohyoid dissection (2) For bilateral submaxillary and submental dissection (3 and 4) For wide unilateral dissection extending to the clavicle

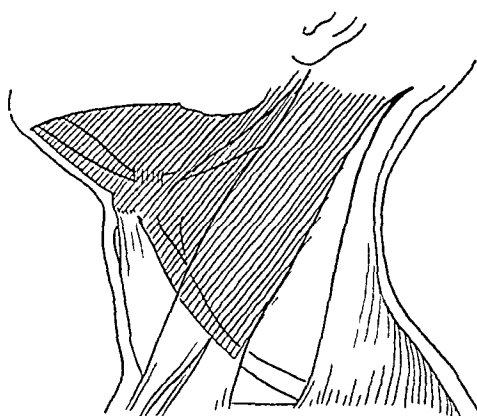


FIG 12—Extent of neck dissection in cancer of the lip, provided that metastases are not palpable is below the level of the carotid bulb. If the middle or lower deep cervical nodes are palpably enlarged the area of dissection should extend to the clavicle

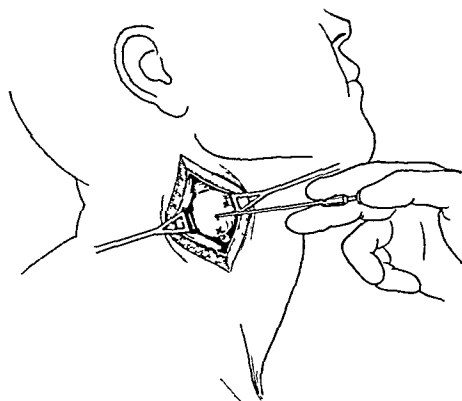


FIG 13—For supplementary irradiation of a cervical metastatic node by gold radon seeds accuracy in the placement and distribution is favored by surgical exposure of the outer surface of the node

procedure, however, which deserve mention. Four of the most useful forms of incision for neck dissection are shown in Figure 11.

The anesthesia, in practically all cases, should be local rather than general, since the higher mortality rates almost invariably are reported from those clinics where general anesthesia, usually rectal, is employed routinely. In properly selected cases, the mortality in neck dissection under local anesthesia should be practically zero. In cancer of the lip, the area of the neck dissection may properly be confined to the submaxillary, submental, and upper deep cervical regions above the level of the omohyoid muscle (Fig. 12). Unless the primary lesion involves the midline, the submental dissection may be limited to one side. Bilateral neck dissection at one sitting had best be limited to the submaxillary and submental regions. If the upper deep cervical areas are to be included, the procedure should be done in two stages at an interval of three to four weeks. The superficial and the deep planes of the dissection should be, respectively, the inner surface of the platysma muscle and the fascia of the deep muscles of the neck. It is best to remove the submaxillary salivary gland, the sternomastoid muscle, and the internal jugular vein. It is impractical to attempt to dissect out and preserve the eleventh cranial nerve. If there is palpable involvement of the middle deep cervical nodes, the area of dissection should extend down to the clavicle.

Radiation Methods for Cervical Metastases in Lip Cancer—One of the most useful radiation technics is fractionated roentgen radiation given through a small portal directly over the node and followed by a supplementary dose of radon seeds. Under such a plan, there is a wide possible variation in technic. The dosage factors and technic described here refer to the employment of the following: 200 k v, 0.5–1.0 Mm Cu filter, 35 cm TSD, and portals 3–5 cm in diameter. The treatment is designed to be given to a single node, to a group, or to each of immediately adjacent nodes. If the nodes are widely separated, it is best to treat each individually. Using portals 3–5 cm in diameter (depending on the size of the node), the fractionated roentgen radiation is administered in daily or thrice-weekly treatments so as to administer 5,000–8,000 r in approximately 18–20 days, and immediately upon the completion of this radiation a supplementary dose of radon seeds is implanted, so calculated as to deliver six to eight SED into the tumor mass (Table II). This plan may be modified in the larger metastatic masses, 5–6 cm in diameter, by fractionating the doses of radon seeds, implanting a lesser amount at weekly intervals during the course of fractionated roentgen radiation. The dosage factors under such modifications are largely empiric and must be learned by experience.

Radon seeds alone may be employed without preliminary external radiation, but the chances of success (especially in the larger masses) are not equal to those under the combination plan, since small errors in dosage and in the placement of the implants are much more significant than when part of the effect is obtained by external radiation. If gold radon seeds alone are employed, according to the method developed by Quick,⁴⁶ the dose is

calculated according to Table II, and should be larger, approximating ten SED in all cases. This method is often more useful and more expedient in the smaller nodes (less than 1.5 cm in diameter).

TABLE II
MILLICURIES IN GOLD SEEDS REQUIRED TO DELIVER SPECIFIED DOSES TO MASSES OF VARIOUS DIAMETERS

Skin Erythema Doses	Diameter of Mass—Centimeters											
	1.0	1.5	2.0	2.5	3.0	3.5	4.0	4.5	5.0	6.0	7.0	8.0
	Number of Millicuries											
5	1.0	2.5	4.0	7.5	10	12	14	17	20	27	35	45
6	1.2	3.0	4.8	9.0	12	14	17	20	24	32	42	54
7	1.4	3.5	5.6	10	14	17	20	24	28	38	49	63
8	1.6	4.0	6.4	12	16	19	23	27	32	43	56	72
9	1.8	4.5	7.2	14	18	22	26	31	36	49	63	81
10	2.0	5.0	8.0	15	20	24	29	34	40	54	70	90
11	2.2	5.5	8.8	17	22	26	32	37	44	59	77	99
12	2.4	6.0	9.6	18	24	29	35	41	48	65	84	108

Radon seeds may be implanted through skin punctures, but then accurate placement is favored by surgical exposure, under local anesthesia, of the outer surface of the node (Fig. 13). Previously administered fractionated roentgen radiation to the node is no contraindication to surgical exposure, even though there is moderate blistering of the skin. Provided that the tissues are handled gently, healing is quite prompt when the incision is made through these blistered areas.

Combination of Surgery and Radiation for Cervical Nodes—Combination methods are indicated particularly in the case of bulky, fluctuant suppurating metastases which are attached to the mandible. Such a lesion is usually inoperable, since its capsule has been perforated and the infected tumor has become attached to the periosteum of the mandible or to the deep muscle layers of the neck. Combination treatment may be given by applying heavy radiation (10,000 rads) plus radon seeds in doses calculated to destroy the growth, following which the condemned mass of tissue, which would otherwise slough, is excised surgically, the wound, ordinarily, being left open to granulate and heal by secondary intention.

In other instances, the major portion of such a secondarily infected and perforated metastasis may be removed surgically by partial or total neck dissection and the infiltrated irremovable portion (often only 1–2 cm in diameter) may be treated by the implantation of radon seeds. The detailed technic, especially with regard to radiation dosage in such cases, is too varied for detailed description.

COMPLICATIONS

Since the lip is not a vital structure, it is to be expected that serious complications seldom occur either as the result of the primary lesion or of its treatment. The most frequent treatment complication (7 per cent) in our series was persistent radiation necrosis at the site of the primary lesion following the implantation of radon seeds. In practically all instances, this

difficulty was due to injudicious dosage or incorrect placement of the implants. In all of these cases, surgical excision of the unhealed area resulted in subsequent healing. In nine cases (2 per cent) where radiation had been employed in the treatment of extensive growths of the lip or metastases under the edge of the mandible, localized osteomyelitis of the mandible developed, necessitating sequestrectomy. Such a complication is often unavoidable in the management of inoperable cancer. In the present series, there were seven postoperative deaths following extensive surgical removal of the primary lesion, the causes of death being pneumonia (two cases), lung abscess (two cases), heart failure (two cases), and septicemia (one case).

Recurrence—Some of the apparent recurrences which take place after either radiation or surgical treatment are actually new cancers arising on other parts of the mucous membrane of the lip. In this series there were apparent recurrences in 22 cases following irradiation and two following surgical excision (6 per cent), and it has been impossible for us to determine exactly how many of these were actually second primary lesions. Of this group, subsequent treatment was successful in 16. Three died of other causes, and in only five of the 24 was treatment ultimately unsuccessful and death due to cancer. The elapsed time between treatment of the primary and the appearance of the second lesion or recurrence ranged from two months to seven years, with an average of 32 months.

FOLLOW-UP

Systematic follow-up of all cases is an integral part of the management of all forms of cancer, so that accurate information of the patient's clinical progress may be recorded for a period of at least five years. The surgeon who undertakes the treatment of a case of cancer places himself under a moral responsibility to keep the patient under observation during the period in which recurrence is likely to take place. For practical purposes, both the total period of observation and the intervals between examinations should vary with the relative malignancy of the anatomic form of the disease, as for instance, patients with cancer of the nasopharynx should be seen at shorter intervals than those with cancer of the lip. For statistical purposes, a five-year period of observation is required in all forms of cancer. In cancer of the lip, the customary intervals between examinations, at the Memorial Hospital, are indicated in Table III.

From the standpoint of the patient, the ostensible purpose of follow-up is the discovery and treatment of recurrences while the disease is still in a curable stage. From the scientific standpoint, another purpose, equally important, is the accumulation of definite knowledge of the progress of the patient and of his actual status at the end of a five-year period, when a final accounting of all cases is made. It is not sufficient that the physician should *believe* that the patient is well and free of disease simply because he has

heard nothing to the contrary. It is necessary to have factual evidence that the patient is alive and free from symptoms. If the patient has died before the end of the five-year period, it is essential to know the actual cause of death and whether there was clinical evidence of disease at the time. If he is living, it is essential to know whether he is free of disease or suffering from recurrent or metastatic cancer. Without dependable data in these respects, statistical reports of end-results have no value. In large series of cases there are, inevitably, some patients who refuse to make return visits and are subsequently lost track of. If they have been free of recurrence

TABLE III
INTERVAL BETWEEN EXAMINATIONS*

After Primary Treatment of Lesion	Frequency of Follow Up Visits
During first 6 months	Every 1-2 mos
During second 6 months	Every 2-3 mos
During the second year	Every 3-4 mos
During the third and fourth years	Every 3-6 mos

* The shorter periods are to be preferred in all cases but it is often necessary to compromise when the patient lives at a considerable distance because of the effort, inconvenience and expense of travel.

for a year or more before they disappear, they may fairly be termed indeterminate cases and subtracted from the total, thereby counting neither for nor against the end-results. If they are lost track of immediately following the initial treatment or before the end of a year, they must be counted as failures, whether or not they were free of disease when last seen. The investigator who subjects himself to such rigid discipline in calculating end-results will be stimulated to renewed effort in tracing lost patients.

Adequate follow-up is mainly a matter of organization and persistent effort. When a patient is discharged following the initial treatment, he should be given a definite future appointment for reexamination. If he does not return at the designated time, repeated appeals should be made by mail and by telephone to the patient himself, to members of his family, and to the referring physician. If these efforts fail, a personal visit by a social service worker may induce the patient to return, or at least furnish positive information as to his physical status. A single letter from the patient or a relative stating that he is free of disease is of little value but continued reports and a final statement, after five years, that he is alive and well can be considered adequate. Before making the final calculations on a series of patients for five-year end-results, renewed attempts should be made to locate all untraced patients. Former addresses and telephone numbers should be checked. Relatives, friends, employers, or the referring physician should be questioned. If these sources reveal no information, local health boards may be appealed to for death records. Frequently an insurance company may be able to furnish pertinent facts. In series of cases now being analyzed at the Memorial Hospital, for which we have access only to these sources of information, we are able to locate between 90 and 95 per cent of all patients,

a proportion which biostatisticians have informed us is satisfactory for statistical purposes

PROGNOSIS

Cancer of the lower lip is one of the least malignant forms of intra-oral cancer. Early lesions up to 1.5 cm in diameter should be capable of cure in practically all cases following proper treatment if the patient is regularly observed and examined for recurrence. Failures often result from inattention to proper follow-up by either the patient or the physician. In this series, the average length of life of the unsuccessfully treated patient was about 38 months after onset. Certain factors influencing the cure rate, calculated on the determinate group, are given in Table IV.

TABLE IV

FACTORS INFLUENCING THE FIVE-YEAR CURE RATE IN 313 CASES (DETERMINATE GROUP) OF CANCER OF THE LIP OBSERVED AT THE MEMORIAL HOSPITAL

1928 to 1934 inclusive

	Total Number of Cases	Number of Five-Year Cures	Per Cent of Five Year Cures
Age in Years			
Below 40	38	31	89
40 to 49	63	45	71
50 to 59	86	57	66
60 and over	121	85	70
Not stated	5	1	
Metastases			
None at any time	196	187	95
Present some time	117	32	27
Present on admission	90	22	24
None on admission	223	197	88
Developed after admission	27	10	27
Bilateral submaxillary	20	4	20
Histopathology (cases in which the primary was treated at Memorial Hospital)			
Squamous carcinoma Grade I	87	73	84
Grade II	143	102	71
Grade III	4	2	50
Grade IV	1	0	0
Ungraded	42	33	75
Spindle cell carcinoma	2	1	50
Size of Lesion			
Under 1 cm	33	33	100
1 to 1.9 cm	118	102	86
2 to 2.9 cm	49	35	71
3 cm and over	60	33	55
Entire lip	5	5	100
Not stated	48	11	23
Position of Lesion			
Upper lip	17	7	41
Lower lip	296	212	71
Associated leukoplakia	70	55	79
Associated syphilis	25	13	52
Primary cases (no treatment elsewhere)	228	175	77
Residual recurrent or metastatic cancer after previous treatment elsewhere			
After radiation alone	32	20	63
After surgery alone	30	12	40
After combination of radiation and surgery	6	2	33
After electrocoagulation or cautery	17	10	59
Total patients with residual or recurrent disease	85	44	52

Age and Sex—From the analysis of the present series, it would appear that the prognosis is best below the age of 40 and over the age of 60. However, since the age-prognosis curve is rather irregular, we suspect that this variation is purely coincidental and that if the series were larger these deviations might be less evident. The treatment of cancer of the lip does not carry with it a high mortality rate, nor do we believe that the age of the patient markedly affects the malignancy of the individual tumor. Since the percentage of females with lip cancer is so small, no conclusive calculation of sex prognosis is possible.

Metastases—Although not always so interpreted, the malignancy factor of any neoplasm depends almost entirely upon its capacity to metastasize. No better illustration of this fact can be found than in the prognosis of lip cancer. From Table IV, it is seen that of the cases which had no metastases at any time, the cure rate was 95 per cent. The failure to cure the remaining 5 per cent depended upon such infrequent occurrences as postoperative deaths, and those rather rare cases of inoperable and incurable, bulky tumors of the lower lip with no evidence of metastasis on admission. The presence of metastases at some time during the course of the disease reduces the cure rate to about 27 per cent. It would appear that the time of development of metastases has little influence on the prognosis, since the cure rate is about the same whether involved nodes are present on admission (24 per cent) or develop later (27 per cent).

Histopathology—Our calculations of the histopathologic prognosis were made only upon those cases in which the primary lesion was treated at Memorial Hospital. Patients who were referred to our clinic with cervical metastases following cure of the primary lesion are not included, since the histologic grading of such cases is often uncertain. As would be expected, the prognosis is best in low grade squamous carcinoma and poorest with the higher Grades II and III.

Size of the Lesion—When the primary lesion is less than 1 cm in diameter, cure may be assured in almost all cases (100 per cent in the present series). As the size of the primary lesion increases, indicating a later stage of the disease and a greater chance of metastasis, the possibility of cure progressively diminishes, but it should be noted that even when the primary lesion is over 3 cm in diameter, the chance of cure is still about 55 per cent. Curiously enough, in the five cases in which the entire lower lip was involved, the cure rate was 100 per cent. The good prognosis in these cases probably depends largely upon the fact that if the patient survives long enough for the primary lesion to involve the whole lip, the tumor is almost always of low histologic grade and apparently incapable of metastasizing, and, therefore, cure depends entirely upon control of the primary lesion.

Position of the Lesion—Growths of the upper lip appear to belong to the group of spontaneous cancers, in contrast to those of the lower lip, in which chronic irritation is usually obvious as an etiologic factor. It is a common observation that such spontaneous cancers are highly malignant as

compared to irritation cancers. Such a theory is supported by the fact that of our 17 patients with primary lesions on the upper lip, only seven (41 per cent) survived five years.

Syphilis—According to our statistics, the prognosis in lip cancer with associated syphilis (52 per cent cure rate) is less than the general average (70 per cent). Since the complications of treatment in lip cancer are so few, it is difficult to interpret this finding, which may be purely coincidental since the number of our cases with syphilis (25) is small.

Status on Admission with Regard to Previous Treatment—Unsuccessful attempts at treatment reduce the possibility of cure in cancer of the lip, as shown in Table IV. The cure rate in those patients (primary cases) who did not receive previous treatment was about average, even when all-comers in all stages of the disease are included. The cure rate was only 52 per cent in the patients referred to us with residual and recurrent disease after unsuccessful treatment elsewhere. Despite the fact that the end-result statistics (70 per cent) could be improved (77 per cent) by the exclusion of such recurrent cases, it is obvious that the truth in regard to this disease is not revealed except by the inclusion of all clinical material.

END-RESULTS

In the present series, the net cure rate in 375 cases is 70 per cent (Table V). As we have previously mentioned, this series consists of a consecutive

TABLE V
FIVE-YEAR END RESULTS IN CANCER OF THE LIP OBSERVED AT THE MEMORIAL HOSPITAL
1928 to 1934 inclusive

This series consists of all histologically proved cases of cancer of the lip both early and advanced admitted during the specified period. Only those patients are excluded who for any reason were unable to return for treatment, palliation and observation in the Out-Patient Department and those who were lost track of within the first month after no more than one or two visits (clinic shoppers).

Total Number of Cases		375
Indeterminate Group		
Dead as a result of other causes and without recurrence	39	
Lost track of without recurrence	23	
Total number of indeterminate results		62
Determinate Group		
Total number minus those of indeterminate group		313
Failures		
Dead as a result of cancer	87	
Lost track of with disease	4	
Living with disease	3	
Total number of failures in treatment		94
Successful Results		
Free from disease after five years or more		219
Five-year End-Results		
Successful results divided by determinate group (219/313)		70%

group of all histologically proven cases of cancer of the lip, both primary and recurrent, which were admitted to our clinic during the years 1928-1934, inclusive. It is the policy of our clinic to accept all ambulatory patients with cancer, no matter how advanced the disease. If the patient is able and willing to return for treatment, palliation, or observation, the case is included

in our records for statistical purposes. Before calculating the net end-results in a given series, we subtract only those cases in which an unfavorable outcome is not due to cancer, or in which the end-result is not definitely known because the patient was lost to follow-up after a year's freedom from disease. In the larger clinics, there are inevitably some patients lost track of, and such an allowance is, therefore, necessary. Such a policy of subtracting the indeterminate cases before calculating net end-results in cancer is followed in the large cancer clinics of the world (Radiumhemmet, Curie Institute). Biostatisticians whom we have consulted state that if at least 90 per cent of the cases in a series are accounted for, the calculations will be sufficiently accurate. In the present series, 93 per cent of the patients have been traced.

There is probably no anatomic form of cancer for which more end-results have been published than for cancer of the lip, but an attempt to compare our figures with those reported in the literature is disappointing. It is regrettable that so many reports, emanating from excellent clinics and made by undoubtedly competent surgeons and radiologists^{20 23 34 38 48 55} should be unsuitable for statistical analysis. An outstanding fault in most publications is the lack of any standard, or definite, period of survival, as, for instance, a certain percentage of patients is said to have survived "from one to seven years,"⁴⁷ with no further data as to the number or proportion surviving for any given period. In many such unsatisfactory reports, it is obvious that the author has included a number of recent cases in an effort to make the total series as large as possible. Unfortunately, such attempts fail to accomplish the intended purpose, since all the figures are vitiated by the introduction of so much inconclusive material. How much more impressive it would be if accurate and conclusive results were given on a smaller group of consecutive cases, all observed for at least a five-year period. Many of the older reports and some of the more recent, even though otherwise suitable, are based upon three- rather than five-year survival periods. In other instances, one finds end-results calculated only on the patients treated with curative intent, without considering advanced cases for whom only palliative measures were possible. Other authors exclude cases recurrent after previous treatment elsewhere. There are also published calculations based upon only those patients "traced" with no accounting for those lost to follow-up, although in some of these the untraced cases make up almost one-fourth of the whole group. Some investigators begin by setting down a certain number of cases and then base their end-results on a much smaller number, with no explanation for the discrepancy. End-result statistics on "early cases," "cases without metastases," or cases "operated upon" are obviously calculated on highly selected groups and do not give the actual cure rate for cancer of the lip, but only the prognosis in various stages of the disease. In every instance, such grouping must necessarily be arbitrary, because any two surgeons would rarely agree exactly on the classification of all cases.

CANCER OF THE LIP

TABLE VI

PUBLISHED FIVE-YEAR END RESULTS ON UNSUCCESSFUL CASES OF CANCER OF THE LIP

	Period Covered by Report	Total No of Cases	Indeterminate		Determinate		Net Five Year Cure Rate Percentage†
			Lost N E D	Died of Other Causes	Died of Disease‡	Five-Year Cures	
Berven ⁴	1900-1923	179				(?)	64.2
Welsh and Nathanson ⁶³	1933	990‡	41		503	446	45
Lacassagne ³¹	1919-1924	68		10	24	34	58
Schreiner and Mattick ⁶²	1914-1927	258§	19	32	140	94	40
Bergendal ²	1914-1930	172	1	35	27	110	80
Martin MacComb and Blady	1926-1934	375	23	39	94	219	70

* This includes patients lost track of with disease and patients living with disease

† Number alive and well divided by the number of the determinate group

‡ Twenty untreated, counted as failures

§ Four untreated, counted as failures

The end-result statistics collected in Table VI are the only ones we have been able to find in which sufficient facts are given so that one can accept the stated cure rate, or so that one can calculate the net end-results from the data which are given. As compared to most serious forms of cancer, it will be seen that these end-result statistics are consistently high.

SUMMARY

This report is based mainly upon an intensive analysis of 375 consecutive cases of lip cancer, all histologically proved, admitted during the seven-year period 1928 to 1934, and includes all patients with cancer of the lip who applied to our clinic during that period, without exclusion of any because of an advanced stage of the disease. In the light of this material, cancer of the lip is discussed from the standpoints of etiology, pathology, symptoms, treatment, and prognosis. The net five-year cure rate in these 375 cases is 70 per cent.

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PERFORATION OF THE CERVICAL ESOPHAGUS WITH THE FLEXIBLE GASTROSCOPE*

CASE REPORT—DIAGNOSIS—TREATMENT

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WITHIN RECENT YEARS, the hazards of endoscopic examination of the stomach and first portion of the duodenum have been greatly reduced by the use of the flexible gastroscope. Thus, a recent questionnaire by Schindler,¹ who devised the instrument, disclosed that only ten serious accidents had occurred in a total of 22,351 cases in which it had been employed. These accidents all consisted of traumatic perforations, eight involving the stomach, one the jejunum, and one the cervical portion of the esophagus. Only the last resulted fatally. In view of the apparent rarity of accidental perforation of the cervical portion of the esophagus with the flexible gastroscope, it appears warranted to report a case which presented a number of interesting and unusual features, and to discuss briefly the diagnosis and management of the condition.

Case Report—B L, white, male, age 40, was admitted to Mt Sinai Hospital, September 23, 1940. The relevant history was one of recurrent episodes of abdominal pain, vomiting, and loss of weight, of approximately five years' duration. Six months previously, he had suffered a severe hematemesis. Diagnostic studies including gastric analysis and roentgenologic examination, performed in the Out-Patient Department, suggested the presence of a diverticulum of the first portion of the duodenum. In an attempt to clarify the diagnosis further, he was referred to the hospital as an ambulatory case, for gastroscopic examination.

On the day of admission, the Schindler flexible gastroscope was introduced under local anesthesia. The gastroscopist stated that after the instrument had been passed downward apparently without difficulty, for a distance of about six inches beyond the upper incisor teeth, a small amount of blood was noted in the patient's mouth. The instrument was withdrawn immediately, and it was noted that the flexible rubber bougie at the distal end of the apparatus was missing. Within a few moments the patient began to complain of pain over the right side of the neck, and palpation disclosed tenderness and crepitation in that area. Surgical consultation was requested immediately.

When first seen by the author, not more than ten minutes after the accident had occurred, the patient complained of severe pain on swallowing. Both sides of the neck were moderately swollen, especially the right. Bilateral crepitation was present and extended from the clavicle to the angle of the jaw. Tenderness was noted over the right side of the neck lateral to the larynx. The diagnosis of instrumental perforation of the upper esophagus was made and immediate operation advised. In order to ascertain whether the missing tip of the instrument had passed downward into the stomach or was lodged in the cervical region, roentgenologic examination was made while the operating room was being prepared. Films of the neck, with the patient in the antero-

* Presented before the Joint Meeting of the New York Surgical Society and the Philadelphia Academy of Surgery, February 12, 1941.

posterior and lateral positions, revealed extensive collections of air in the cervical tissue planes and in the retropharyngeal and retro-esophageal space (Figs 1 and 2) On the right side, opposite the lower cervical and first dorsal vertebrae, the missing bougie was seen with its tip pointing *cephalad*

Operation—This was performed, under local anesthesia, approximately three-quarters of an hour after the accident occurred An incision was made along the anterior border

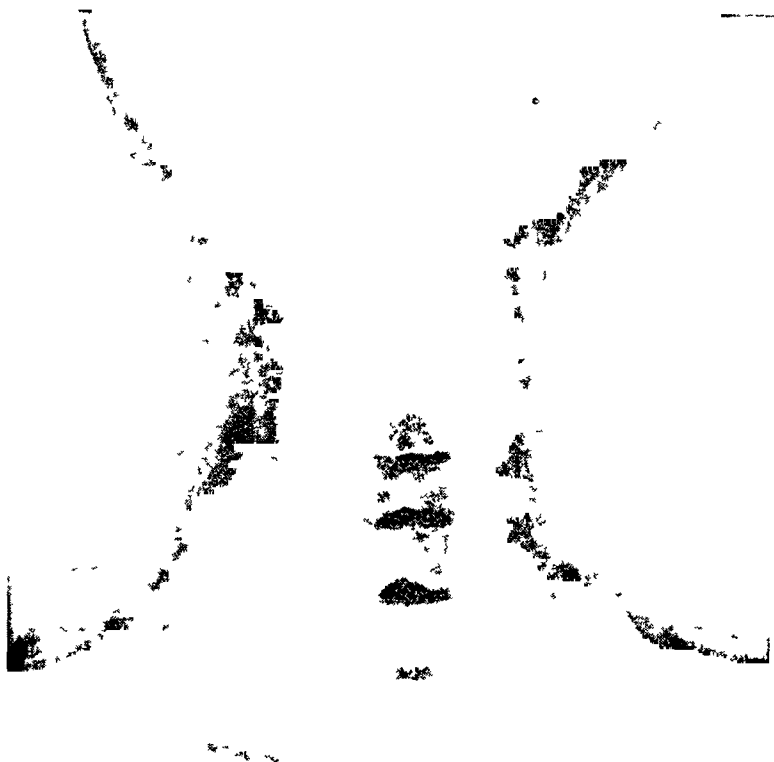


FIG 1—Anteroposterior view. Note extensive subcutaneous emphysema, and air dissecting between the various tissue planes. The missing bougie lies at the root of the neck with its distal end pointing *cephalad*. Note the distance between the bougie and the trachea. The button over the right clavicle lies on the skin.

of the right sternomastoid muscle, from a point above the level of the larynx down to the suprasternal notch. The sternomastoid muscle and carotid sheath were retracted laterally, the anterior belly of the omohyoid traversed, and the margin of the right lobe of the thyroid gland exposed. The latter then was mobilized and retracted medially to expose the lateral aspect of the esophagus.

Everywhere within the operative field the areolar tissue between the muscle planes was distended with bubbles of air. No discoloration was noted however. The missing tip of the gastroscope was discovered at the root of the neck, alongside the esophagus, and was removed. The esophagus was then exposed freely and inspected. About two inches above the level of the foreign body an irregular laceration, approximately one-half inch long and with everted edges, was found in the right posterolateral esophageal wall. In view of the fact that the edges of the defect were bruised and ecchymotic it was deemed unwise to close the latter by suture. Accordingly, a small iodoform packing was placed down to the opening and brought out at the lower angle of the incision. Another small iodoform packing was placed alongside the esophagus, at the entrance to the superior mediastinum, and was also brought out through the lower part of the wound. The subcutaneous tissues and skin were closed loosely with interrupted sutures.

PERFORATION OF ESOPHAGUS

An intravenous infusion of 1,000 cc of 5 per cent glucose solution was begun after operation, and a Levin tube was introduced into the stomach for purposes of feeding. Sulfanilamide was administered, in 1 Gm doses every four hours, for 48 hours. The packing which had been placed down to the esophageal laceration was shortened on the third postoperative day and removed the following day. The lower packing was shortened on the fifth day, and removed 24 hours later. The Levin tube was removed on the



FIG 2—Lateral view. Note particularly, air in the retroesophageal and retropharyngeal spaces and the widening of these areas. Air extends upward to the base of the skull. The bougie lies anterior to the esophagus, and lateral to it (as demonstrated in the anteroposterior view).

sixth postoperative day, and the patient placed upon a soft diet, which he took without difficulty. Convalescence was uneventful, and he was discharged on the eighth postoperative day, with the wound healed. At no time following operation was there evidence of leakage from the esophagus.

Five weeks later, barium studies revealed slight irregularity in the outline of the posterolateral surface of the esophagus at the site of previous injury. No other abnormalities were noted. At the present time (five months after operation) the patient is entirely free of symptoms referable to the esophageal trauma, and roentgenologic examination of the esophagus is negative (Fig 3).

COMMENT—The rubber bougie, which forms the tip of the flexible gastroscope, is cemented to the adjacent metal portion of the instrument, and

is also fixed to it by wire which is incorporated within its substance. Its position when found in the periesophageal tissues, with its distal end pointing *cephalad*, would seem to indicate that the bougie became sharply angulated at its point of junction with the metal portion as the instrument was being



FIG 3—Four months postoperative. Roentgenogram taken after administration of a thin barium mixture. Note the normal contour of hypopharynx and esophagus, and normal retropharyngeal and retroesophageal spaces.

passed. The result was that the metal end, no longer protected by the soft bougie which normally advances ahead of it, penetrated the esophageal wall and passed into the tissues of the neck. In view of the fact that the gastroscopist reported that no difficulty had been encountered, and that undue force had not been employed as the instrument was passed, the bougie could have become so sharply angulated only if it were loose. Its complete detachment, outside the esophagus, probably occurred as the instrument was being withdrawn.

Discussion—Personal observation of 20 cases of accidental perforation of the cervical portion of the esophagus, both by instruments and ingested foreign bodies (usually chicken and fish bones) has demonstrated that all such lesions are not only potentially serious but are often a threat to life. Because of the direct anatomic continuity between the retro-esophageal space and the posterior compartment of the superior mediastinum, the most common cause of death is mediastinal infection. The initial periesophageal infection may assume the form of a phlegmon or of an abscess. A phlegmon is usually

a diffuse lesion which displays little tendency to localize and quickly extends downward into the mediastinum. An abscess, on the other hand, usually begins as a fairly well-localized lesion, but unless evacuated fairly promptly may subsequently extend downward into the mediastinum. The following case cited by Schindler,¹ although not observed by him personally, illustrates this point well.

In brief, four hours following gastroscopy, with the flexible instrument, the patient developed symptoms consisting of pain in the neck, dysphagia and fever. Marked swelling about the left side of the neck and subcutaneous emphysema (*indicative of actual perforation of the esophagus**), were detected next morning. Because of "improvement" in the patient's condition soon thereafter, conservative therapy was employed. On the eighth day, however, the diagnosis of "abscess of the left hypopharyngeal region" was made. On the next day, the patient developed dyspnea and cyanosis, necessitating an emergency tracheotomy. As the trachea was exposed, large quantities of pus welled into the wound and the patient succumbed on the operating table. The significant findings at autopsy consisted of a perforation of the posterior esophageal wall at the level of the seventh cervical vertebra and an adjacent large mediastinal abscess. The case illustrates very well a frequent result of the conservative treatment of patients with gross perforations of the cervical portion of the esophagus.

At the present time, a difference of opinion exists in regard to the treatment of traumatic perforations of the cervical portion of the esophagus. The chief disagreement appears to center about cases in which the perforation appears to be small, and those in which there is doubt as to whether penetration of the esophageal wall is complete. It has been demonstrated that, in certain cases, a cervical periesophageal abscess may evacuate itself spontaneously into the esophagus through the original pathway of injury, or may be evacuated into the esophagus by endo-esophageal instrumentation. While, unquestionably, such a fortunate outcome may, at times, be noted, personal observation has indicated that it is the exception rather than the rule, and that more frequently the infection extends downward into the mediastinum and results in the patient's death. While it is not the purpose of this communication to discuss, at length, the treatment of actual small perforations or suspected perforations of the cervical esophagus, it may be stated, categorically, that the patient's interests are best served by prompt external surgical exploration rather than by a policy of "watchful waiting." Thus, if actual perforation is present, adequate surgical drainage may be afforded. On the other hand, if the penetration of the esophagus proves to be incomplete, exploration, as described, is a relatively simple procedure which is well tolerated by the patient.

In contradistinction to small perforations or suspected perforations of the cervical portion of the esophagus, there can be little discussion concerning

* Italics mine (A S W T)

the necessity for prompt operation in cases of gross perforation associated with subcutaneous emphysema or with roentgenologic evidence of air in the periesophageal tissues. In such cases the likelihood of serious consequences is great, since leakage of infected material from the esophageal rent is apt to be more free and pathways of extension of infection are opened, as air dissects its way along the tissue planes, especially in a downward direction. In cases in which subcutaneous emphysema is not noted, the diagnosis of perforation can be made on roentgenologic examination of the neck. Films should be taken in the anteroposterior and lateral planes, with the patient in the erect position. The lateral view is particularly important, in so far as it is the only one in which the retropharyngeal and retro-esophageal space can be visualized. Since air escaping from the upper esophagus enters these areas first, the visualization of the latter is essential to early diagnosis. It is to be emphasized that the quantity of air seen in the retropharyngeal and retro-esophageal space need not be great and that the presence of only a bubble or two suffices to establish the diagnosis.

Once the diagnosis of perforation has been made, prompt operation, consisting of exposure and treatment of the esophageal rent through an external cervical incision under local anesthesia, is recommended. As has been stated previously, it is fully appreciated that at times certain patients may recover following more conservative therapy. However, should a patient under conservative therapy develop a descending infection of the mediastinum, as happens not infrequently, the surgical problem becomes much more complicated and the prognosis considerably more grave. In view of these dangers and the negligible risk involved, there appears to be little question as to the wisdom of early operative treatment.

SUMMARY

An unusual case of accidental perforation of the cervical portion of the esophagus with the flexible gastroscope, is presented. The rubber bougie, which constitutes the distal portion of the instrument, became detached and remained lodged in the neck after the gastroscope was withdrawn. The diagnosis of free perforation of the esophagus was made clinically, and confirmed by immediate roentgenologic examination, which disclosed a large quantity of air in the soft tissues of the neck and the missing bougie lying free in the periesophageal tissues at the root of the neck. Prompt operation was performed through an external approach, the foreign body removed, and the perforation cared for. Recovery was uneventful, the patient being discharged eight days after operation, with the wound healed. When last observed, approximately five months after operation, he was entirely free of symptoms referable to the esophageal trauma and roentgenograms were negative.

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DISCUSSION —DR JOHN B FLICK (Philadelphia, Pa) —I have operated upon two patients for mediastinal suppuration following esophagoscopy. They illustrate what may happen when periesophageal infection occurs following injury to the cervical esophagus and operation is delayed. Both were operated upon late, following the injury. Their histories are of some interest and will be recited briefly. The first patient, a female, age 46, had a bronchoscopy and esophagoscopy performed September 1, 1936. These examinations were negative except for a tendency to spasm at the level of the cricopharyngeal muscle on passage of the esophagoscope. That evening, her temperature rose to 102° F, and she developed pain in the region of the sixth cervical vertebra. The following day she had some substernal pain and her leukocytes rose to 15,500. From then on, until after operation, she had a septic temperature. I saw her 25 days after the esophagoscopy, and, under local anesthesia, through a posterior incision, with resection of segments of the fourth, fifth and sixth ribs, drained a large mediastinal abscess on the right side. Ultimately, she made a complete recovery.

The second patient, a female, age 59, had an esophagoscopy performed, under general anesthesia, May 4, 1938. The following day her temperature rose to 102° F, her leukocyte count to 19,000, and she complained of pain in her neck, back and chest. She had difficulty in swallowing, and dyspnea. Because of dyspnea, a tracheotomy was performed, but the dyspnea was not relieved. I saw her seven days after the esophagoscopy, and, under local anesthesia, exposed the upper ribs posteriorly, on the right side. The patient, already in desperate condition, died soon after the operation was begun. However, exposure was continued.

An abscess was opened and foul-smelling pus and gas, under pressure, escaped. A finger introduced into the abscess cavity could be passed across the bodies of the vertebrae to the left side. The abscess cavity extended upward to the level of the first rib and downward to the level of the fifth rib posteriorly. The esophagus could be seen and had been pushed forward. The pleural cavity was not opened. On further examination, with a finger in the abscess cavity and the other hand palpating the base of the neck on the right side, it was evident that the abscess could have been drained by an incision similar to that employed in exposing a diverticulum of the esophagus. The drainage, however, would not have been as satisfactory as through the posterior exposure.

Many surgeons have called attention to the necessity for early drainage through the neck in cases of injury to the cervical esophagus, yet this is by no means always undertaken. Gabriel Tucker has warned of the presence of osteophytes on the bodies of the cervical vertebrae in some individuals which predispose to injury to the esophagus during esophagoscopy. He insists upon lateral roentgenologic studies of the cervical spine in all patients before esophagoscopy. Too much stress cannot be put on the necessity of early operation and drainage through the neck in cases of injury to the cervical esophagus. Drainage should be undertaken as soon as injury and infection are suspected, and before a mediastinal abscess has developed. A rising leukocyte count, emphysema in the tissues of the neck, and a rising temperature following trauma due to instrumentation, or to foreign body, are sufficient evidence to warrant operation.

The use of sulfanilamide and of zinc peroxide should be of value in treating these infections.

ACTUAL HOLDING POWER OF VARIOUS SCREWS IN BONE

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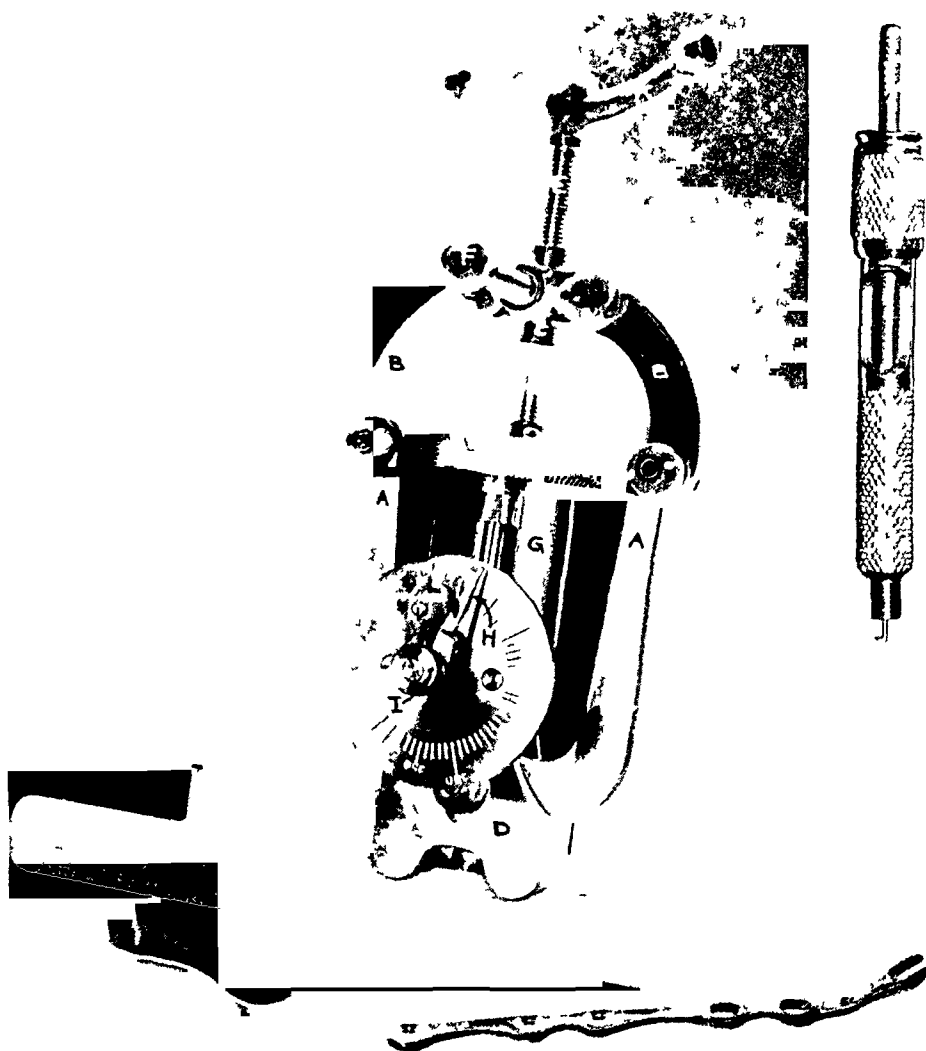
IN THE CONVICTION that most of the difficulties encountered in bone plating are mechanical rather than surgical or physiologic, a comprehensive study was undertaken of the factors involved. The first phase of the work was reported¹ in December, 1938, wherein a simple jig was described for centering the drill point in the hole of a plate. The jig also acts as a very effective depth gauge. The present discussion has to do with the actual holding power of various screws in bone, the determination of the correct drill size for each of the screws, and the effect of time on the holding power of the vanadium, stainless steel, and Vitallium screws.

The Method—The evaluation of the holding power of screws has, in general, been relatively subjective and inexact. It was expressed in terms of ease of application—whether the screw went in with much or little resistance. By its very nature, this was an inexact determination and merely the indication of an impression. We have made this determination an exact one. At first, plates made of spring steel were bent so that with the screws seated the spring of the plate would exert a pull on the screws. Several of these plates were put in dogs with different screws at either end. This method was soon abandoned because the plates, which were made of high carbon steel, corroded and broke. It was then decided to use a noncorroding plate of Vitallium, after cutting a section from the bone. In this manner, the whole weight of the dog was transmitted through the screws. Thus it was possible to show in an indirect way that the end of the plate with fine threaded screws broke loose more frequently than the end plated with the coarse threaded screws. But again this method was inexact and resulted in a high dog mortality.

Finally, it was suggested that a method of extracting screws from bone be devised which would measure the pull required. Such an instrument was constructed by an interested group of engineers (Fig 1). It consists of a vise-like pair of arms which grasp the head of the screw, pulling on the screw as force is applied to the threaded handle. This pull is transmitted through a heavy spring, the force exerted being indicated on a dial. By means of this machine, a pull of 525 pounds could be exerted and, after being calibrated accurately in a physical testing laboratory, an exact measure of the holding power of the screws was possible. As first constructed, this screw puller was capable of only 325 pounds pull, as we had thought this would be sufficient. Then it was increased to 425 and finally to 525 pounds. Even then we were unable to extract some screws anchored in only one cortex of a human bone.

When this method was first used, it was discovered that there was occa-

sionally a wide variation in holding power of a given screw in the shaft of the same bone, despite the fact that the same size drill was used and the screws were applied with equal ease. An additional variable which had not been controlled was the thickness of the cortex. After several attempts, a depth gauge was devised which measures the thickness of the cortex with an accuracy



EXTRACTOR USED IN ESTIMATING THE HOLDING POWER OF THE VARIOUS SCREWS

FIG 1—The device as shown by the photograph consists of a pair of sliding jaws (A), connected by links (B) and a cross head (C), a stationary rest (D), screw (E), handle (I), and a tested spring balance (G). The spring balance is provided with a set pointer (H) for noting the maximum load. For a test, the set pointer is first brought into zero position by turning the knob (I). The device is then placed in proper position over the screw to be tested. The screw is gripped and tension on the screw is applied by turning the screw handle (K), the pointer (L) then indicates the pressure in pounds by means of rack and pinion to the dial. When the screw is extracted, the pointer (L) will move back to the zero position, but the set pointer (H) will remain in place to show maximum load in pounds.

FIG 2—(insert) Depth gauge which permitted an accurate measurement of the thickness of the cortex through each drill hole, before a screw was inserted.

of $1/64$ inch (Fig 2). Readings are taken directly from the center piston. A lock screw at the top of the instrument permits readings after removing the micrometer gauge from the bone. It will be seen later that a slight varia-

tion in cortical thickness may make a large variation in the holding power of the screw, 0.093 inch altering the holding power as much as 80 pounds

We have determined the actual measurements of the several screws used in this study and have indicated the theoretically ideal drill size (equal to the root diameter) Table I gives the outside diameter, the root diameter, threads per inch, and the theoretically ideal drill size

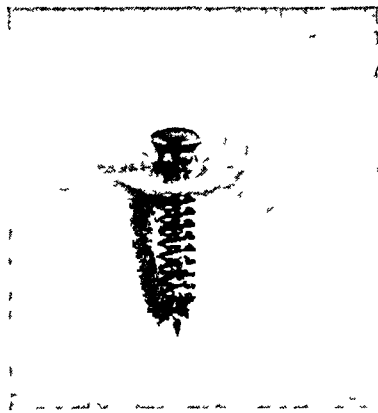


FIG 3—Frequently the screws did not just pull out on being extracted but like the one here shown helped themselves to a 'button' of bone. Obviously the holding power of such a screw is the strength of the cortex of the bone

It would be impractical, and useless, to give the details in regard to all the 1,000 and more screws pulled during this study but illustrative experiments will be presented. By means of the method described, the holding power of different types of screws was determined in the fresh animal, cadaver, and human bones, either following autopsy or amputation. Then the ideal drill size for each screw was determined, as well as a series of extractions showing the holding power when root size drills were used.

Holding Power in Dog Bones Using Root Size Drills—The absolute holding power of four different screws was determined in the bones of freshly killed dogs, and the relative holding power of the different screws compared with special reference to any difference between the fine and the coarse threaded screws. Table II indicates the holding power in one cortex, the

TABLE I

Screw	Diameter Outside Size	Diameter Root	Threads Per Inch	Root Size Drill
Vitallium (fine)	0.138 in	0.104 in	32	37
Vitallium (coarse)	0.144 in	0.104 in	20	37
Sherman	0.134 in	0.102 in	30	37
Zimmer	0.166 in	0.104 in	18	37
Parker Kalon	0.137 in	0.097 in	20	41
Venable Stuck	0.136 in	Tapered	18	
Wood	0.120 in	Tapered	20	

thickness of the cortex in 1/32 inch, and the holding power per 1/32 inch. All these readings are in pounds.

TABLE II

Screw	Actual Holding Power	Thickness of Cortex	Holding Power Per 1/32 in of Cortex
Vitallium (fine)	141 lbs	3/32 in	47 lbs
Sherman	204 lbs	4/32 in	51 lbs
Vitallium (coarse)	156 lbs	3/32 in	52 lbs
Parker Kalon	300 lbs	4/32 in	75 lbs

These results show very little difference between the fine and coarse threaded Vitallium screws and do not confirm our supposition that coarse threaded screws (in the case of Vitallium) should hold more than a fine

threaded screw. Nevertheless, when the Sherman or Vitallium fine screws are compared with the coarse Parker-Kalon screws, a very definite difference is noticed. The similarity in holding power of the two Vitallium screws is due, we believe, to the nature of Vitallium. This particular alloy is so hard that it cannot be machined. Consequently, it has to be cast and the screws do not have as sharp cutting edges, so their insertion into a small hole is more difficult.

We believe the greatest advantage of the coarse, and, therefore, deeper threaded screws, is in their larger allowance for variation in the size of the hole in the bone. Carnes³ has made enlargements of photographs of drill-holes in bones and they are seldom round. It is humanly impossible to hold either the bone or the drill absolutely stationary, and it is obvious that the finer the threads of the screw the more accurate the drill-hole must be to obtain anything like a maximum engagement of bone.

Holding Power in Cadaver Bones—The tibia and humerus of a well-preserved cadaver were used in this experiment, which was designed to demonstrate the difference between fine and coarse threaded screws in human bone, using a root size drill. Again it was difficult to insert the Sherman fine screws, but the Parker-Kalon coarse screws uniformly went in well (Table III).

TABLE III

TIBIA

Screw	Actual Holding Power	Thickness of Cortex	Holding Power Per 1/32 in Cortex
Sherman	240 lbs	5/32 in	48 lbs
Parker-Kalon	375 lbs	5/32 in	75 lbs

HUMERUS

Sherman	180 lbs	4/32 in	45 lbs
Parker-Kalon	500 lbs	5/32 in	100 lbs

In this experiment, as in all others presented, the figures given are average figures—averages of at least six screws extracted from each bone. In the cadaver experiments, the Parker-Kalon screws uniformly caused marked splintering of bone when extracted, while the fine screws left a smooth hole. Several of the Sherman screws stripped the bone while being inserted. These were not included in the averages shown.

Holding Power of Screws in Fresh Human Bone—Screws were applied in the femora of a man, age 76, who had died two hours previously. He had been bedridden for six months with a carcinoma of the prostate. His emaciation was extreme. In this series, as in others, a minimum of six screws of each type was used (Table IV).

The Vitallium screws were difficult to apply well in this experiment. One of the Vitallium screws broke at the head during extraction at 260 pounds. Even though there was considerable demineralization, as demonstrated roentgenologically, the holding power of these screws was high, the coarse threaded stainless steel screws holding considerably more than the coarse Vitallium

TABLE IV

Screw	Actual Holding Power	Thickness of Cortex	Holding Power Per 1/32 in Cortex
Vitalium (fine)	240 lbs	5/32 in	48 lbs
Vitalium (coarse)	270 lbs	5/32 in	54 lbs
Sherman	245 lbs	5/32 in	49 lbs
Zimmer	350 lbs	5/32 in	70 lbs
Parker-Kalon	335 lbs	5/32 in	67 lbs
Venable Stuck	260 lbs	4/32 in	65 lbs

screw The Venable screw held well in this experiment, and went in well (Fig 3)

Holding Power in Child's Bone—We were fortunate in obtaining the recently amputated leg of a girl age eight These determinations were made on the lower third of the child's tibia, which had been amputated for osteogenic sarcoma (Table V)

TABLE V

Screw	Actual Holding Power	Thickness of Cortex	Holding Power Per 1/32 In Cortex
Vitalium (fine)	75 lbs	3/32 in	25 lbs
Sherman	126 lbs	3/32 in	42 lbs
Zimmer	153 lbs	3/32 in	51 lbs
Parker-Kalon	168 lbs	3/32 in	56 lbs

The holding power of screws is definitely less in a child's bone, particularly with the fine threaded screws

Machine Screws Versus Wood Screws—The machine-type screw was long ago advocated for bone work by Sherman Nevertheless, wood screws are still being used, for the very good reason that they are easy to apply However, it seems to us that a wood screw is poorly designed for holding plates, at least, because of its taper In applying any screw, it is necessary to drill a hole approximately equal to the root diameter at the base of the screw If the drill-hole be smaller than this, the bone is subjected to undue pressure resulting in fracturing or pressure necrosis This results in a loss of holding power However, with a drill-hole equal to the root diameter at the base of a tapered screw, the threads near the tip will not engage any bone and the screw will suffer a loss of holding power To confirm these views, a number of screws were extracted from human bone, using machine screws and ordinary wood screws (Table VI)

TABLE VI

MACHINE SCREWS <i>Parker-Kalon</i>			WOOD SCREWS		
Actual Holding Power	Cortical Thickness	Holding Power Per 1/32 In Cortex	Actual Holding Power	Cortical Thickness	Holding Power Per 1/32 In Cortex
400 lbs	10/32 in	40 lbs	240 lbs	10/32 in	24 lbs
350 lbs	9/32 in	39 lbs	160 lbs	8/32 in	20 lbs
420 lbs	10/32 in	42 lbs	180 lbs	7/32 in	26 lbs
400 lbs	8/32 in	50 lbs	140 lbs	8/32 in	17 lbs
43 lbs average			22 lbs average		

These results do not agree with Hawley's⁴ conclusion that tapering screws hold best, but he insists the threads must be wide and deep, the screws long and penetrating, these factors are so essential that they more than outweigh any slight loss from the tapering of his screws

Cortical Versus Cancellous Bone—All our determinations, up to this point, have been made upon the cortex of the bone, where the majority of screws are used in surgery. However, the use of screws around joints is becoming more common, and we were anxious to discover the difference in the holding power of the screws in porous bone as compared to compact cortical bone. Table VII shows a striking loss of holding power in cancellous bone as determined upon a human leg. Here, it is obvious that the coarsest possible thread is advisable to insure any appreciable holding power.

TABLE VII

Screw	Actual Holding Power	Depth of Insertion	Holding Power Per 1/32 in Cancellous Bone
Sherman	64 lbs	16/32 in	4 lbs
Parker-Kalon	144 lbs	16/32 in	9 lbs
Zimmer	224 lbs	16/32 in	14 lbs

It was also found that if only the thin overlying cortical bone was drilled and the screw allowed to cut its own way into the cancellous bone, the holding power of the screw was nearly doubled.

Correct Drill Size—The correct drill size is a factor of major importance, since the holding power of a screw is in direct proportion to the amount of bone engaged by the threads. When we attempted to find authentic data on drill size, we were surprised by the paucity of information in the literature, and the complete omission of this subject from the catalogues of the various manufacturers of surgical supplies. Apparently, it was omitted because it was not known. One of the things we have tried to evaluate, therefore, is the optimum drill size for each screw.

From a theoretic standpoint, it seemed to us that the correct drill would be one which made a hole equal to the root diameter, or shank of the screw. A drill larger than this would reduce the amount of bone engaged by the threads and a smaller one would make insertion of the screw impossible. The only screw commonly used in bone work for which a drill size is mentioned (Sherman's) has a root diameter of 0.102 inch, and an outside diameter of 0.138 inch. The drill size recommended by him is a No. 32, measuring 0.118 inch, which leaves but 0.020 inch of thread to engage bone, or about 55 per cent of the total thread depth. Cotton² recommends for this screw a No. 30 drill, having a diameter of 0.128 inch. The discrepancy here results in a loss of some 70 per cent of potential holding power.

It was difficult, or next to impossible, to start some of the screws with a drill as small as the root diameter. These screws were inserted under ideal conditions, with the bone well-exposed and held firmly. Such conditions do not obtain in the operating room where fractures are difficult to hold and wounds deep. We wished therefore, to determine the optimum drill size for

each screw, one which permits easy application and affords maximum holding power

Extractions were made from a series of drill-holes, varying in size from the root diameter to approximately the outside diameter of the screw. These were done in fresh dog and human bones, the results with the two types of bone, while varying in total holding power, correlated nicely (Table VIII)

TABLE VIII
DETERMINATION OF OPTIMUM DRILL SIZE
Holding Power in Pounds Per 1/32 In. Cortical Bone with Various Drills

Drill Size	37	36	35	34	33	32*	31	30	29	Holding Power with Optimum Size Drill
Sherman	46	58	46	58	58	62	62	47	36	62
Vitalium (fine)	45	45	50	50	62	60	62	50		62
Vitalium (coarse)	50	50	51	48	60	60	60	53		60
Zimmer	70	68	70	72	70	75	75	70		75
Parker Kalon	71	70	72	80	75	60	64	52		80
Venable Stuck (9/64 in.)	16	15	18	18	17	16	13			18
Drill Size	47	46	45	44	43	42				
Venable Stuck (7/64 in.)	15	17	16	15	14	14				17

* Drill sizes over columns containing highest numbers (in bold faced type) afforded maximum holding

Each drill was checked by a micrometer, and a variation of 0.002 inch to 0.00 inch was found. While it seemed correct theoretically, to use a drill size equal to the root diameter of the screw, it became obvious that this size drill made the application of most of the screws too difficult for practical purposes. This was particularly the case with the fine threaded screws and the Vitalium screws—not as apparent with the Zimmer and Parker-Kalon screws.

In most cases, there was an actual increase in the holding power of the screws when an optimal rather than root size drill was used, although the former is always slightly larger. Probably this is because the larger drill makes the application of the screw easier and less likely to cause stripping of bone as the screw is inserted.

Another fact brought out in Table VIII, which seems important to us, is the variation in holding power of the Vitalium and Sherman screws as compared to the stainless steel coarse screws, as different sized drills are used. This further emphasizes the point made above, namely, with the Vitalium and Sherman screws the application is difficult with small drills and one screw may go in well while the next may be inserted only with great pressure. To insure good application with these screws the larger size drills are necessary.

The effect of time on the holding power of these screws is seen by the curves shown in Chart I, which are self-explanatory. It is obvious that loss in holding power with either stainless steel or Vitalium screws is too slight to be of clinical significance, particularly, when we keep in mind the fact that most fractures which are immobilized in fair position exhibit bony union in eight weeks. Table IX shows the percentage of loss in holding power at the end of ten weeks, after which screws will have served their purpose.

HOLDING POWER OF SCREWS IN BONE

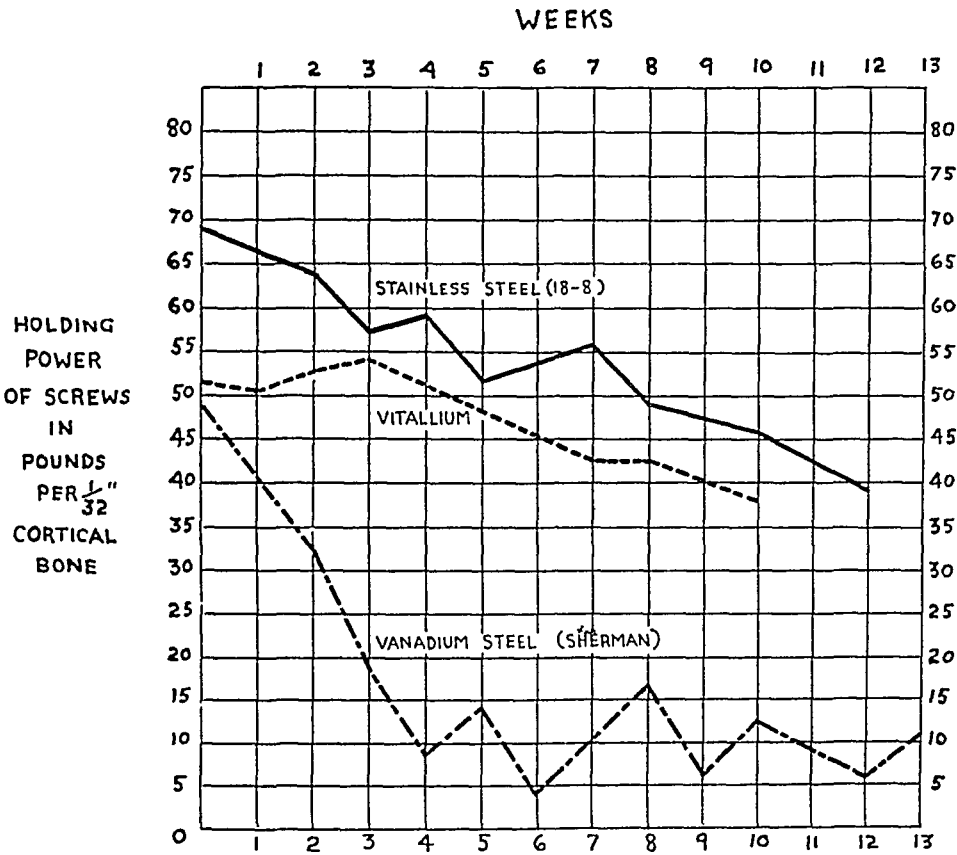


CHART I

TABLE IX

EFFECT OF TIME ON HOLDING POWER OF SCREWS

Type of Metal	Initial Holding Power n Lbs Per 1/32 in Cortical Bone	Change in Holding Power by Weeks													Percentage Loss of Holding Power in Ten Weeks
		1	2	3	4	5	6	7	8	9	10	11	12	13	
Vanadium steel	49	40	34	19	9	14	4		17	7	13		5	11	74%
Vitallium	52	51	53	54		48		43	43		38				27%
Stainless steel	69		64	57	59	51		56	49		46		39		34%

Table X shows drill measurements, and is included here for convenience

TABLE X

Drill No	Diameter in Inches
47	0 0785 in
46	0 0810 in
45	0 0820 in
44	0 0860 in
43	0 0890 in
42	0 0935 in
37	0 1040 in
36	0 1065 in
35	0 1100 in
34	0 1110 in
33	0 1130 in
32	0 1160 in
31	0 1200 in
30	0 1285 in
29	0 1360 in

Our screw puller was not designed for, nor capable of, pulling the screws used in fixation of fractures of the femoral neck, the strength of these devices has been thoroughly investigated by Compere⁵

SUMMARY AND CONCLUSIONS

The variable mechanical factors of applying metal screws in bone have been discussed with the view of discovering the possible sources of error and failure in obtaining maximum holding. Sufficient data has been presented to demonstrate our conviction that the mechanical aspects of this engineering problem are of great importance. While it has been shown that a coarse threaded screw is superior in holding power to a fine threaded screw, it has also been shown that the character of the metal employed modifies this difference. Particularly, with cancellous bone, it is evident that the coarser threads are more advantageous. A series of original determinations have been made to ascertain the correct drill size for the screws tested (Table XI)

TABLE XI

Screw	Correct Drill Number	
Sherman	31 or 32	
Vitallium (fine thread)	31 or 32	
Vitallium (coarse thread)	31 or 32	The larger size should be used in especially hard bones otherwise the smaller is recommended
Zimmer	31 or 32	
Parker Kalon	33 or 34	
Venable Stuck (9/64 in.)	34 or 35	
Venable Stuck (7/64 in.)	35 or 36	

The holding power of screws made of stainless steel or Vitallium does not diminish sufficiently in ten weeks to be of clinical importance.

If the various factors are carefully controlled, six screws used in applying a plate to a "normal femur," set through both cortices, could resist a pull of as much as one and one-half tons¹

Since the Zimmer Manufacturing Company have changed their screw sufficiently, since our work was done, the results as recorded do not now apply.

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MORBID INFLUENCES IN INTESTINAL OBSTRUCTION AND STRANGULATION

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INTESTINAL OBSTRUCTION remains one of the most rapidly lethal of surgical diseases. Scuddei, Zwemer and Whipple,²⁹ in 1938, studied a series of 2,150 cases of acute intestinal obstruction and strangulation collected from a number of sources. When herniae and tumors had been excluded from that series, there remained 632 cases, of which 45 per cent had proved fatal. In spite of phenomenal progress in other branches of abdominal surgery, the mortality of acute intestinal obstruction remained at a high, and almost unchanged, level for more than 30 years after the beginning of the present century, and the disease is still a challenge both to the surgeon and to the experimentalist.

The incalculable number of experiments in intestinal obstruction which have been performed during the last quarter of a century have, however, not been fruitless. As a direct result of animal and clinical experimentation, two powerful new weapons have been added to our therapeutic armamentarium—the nasal suction tube and the intravenous saline drip. Powerful as these weapons are, it is wise to realize their limitations. Nasal drainage and intravenous saline are beneficial in most cases of acute intestinal obstruction, and may be continued with benefit for days in simple occlusion of the bowel, for example, and in adynamic ileus. In cases of strangulation, on the other hand, the need for operative relief is much more urgent. It is often difficult to distinguish simple occlusion from strangulation clinically, and to persist with conservative measures in a case of internal strangulation is to court disaster. I have been impressed by more than one case of adhesive obstruction, treated by suction drainage and saline infusion for 24 hours or more, only to present at operation a strangulated and devitalized bowel, 24 hours of delay may mean the difference between viability and gangrene. It is conceivable that, while the present vogue for prolonged preoperative decompression and saline administration may be expected to reduce the mortality of simple intestinal occlusion, it may actually lead to an increase in the mortality of internal strangulation.

Even in simple occlusion of the bowel, patients still die with sufficient frequency to raise the suspicion that we have something yet to learn of the lethal mechanism of the disease. It may be that our administration of saline is too haphazard and inexact, dosage formulae, such as those elaborated in the Department of Surgery of the University of Michigan,¹⁴ certainly merit wider adoption. Whatever the explanation, frequently a patient suffering from intestinal obstruction is lost in spite of preoperative nasal suction drainage, in spite of forced intravenous salines, and in spite of an apparently successful operation. In these fatal cases, the chloride content of the blood may be at or

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near a normal level just before death. One is forced to the conclusion that depletion of water and chlorides is not invariably the sole lethal factor.

In the literature of intestinal obstruction, there is a frequent conflict of theories, and even of experimental observations. This is in great part due to the complexity of the subject. Intestinal obstruction is not a single disease, but a group of diverse diseases, a theory of the cause of death in duodenal occlusion is not applicable to volvulus of the sigmoid colon. It follows, therefore, that each variety of obstruction must be separately studied, and the more exact our pathologic classification is, the more accurate are our observations and deductions likely to be.

The following classification is sufficiently inclusive for clinical purposes, and detailed enough to be a basis for experiment. It must be remembered, however, that pure forms of obstruction, though easily produced in the experimental animal, are relatively rare in clinical practice. In strangulated hernia, for example, the strangulated loop is also a closed loop, the bowel above the strangulation is occluded at the hernial ring, just as in low small intestine obstruction, ultimately, the whole small intestine dilates above the obstruction, and the vomiting of high obstruction is superadded upon the effects of a relatively low obstruction, finally, after relief of the strangulation, the affected loop of bowel may fail to recover its peristalsis, and we may have strangulation, small intestine obstruction, closed loop obstruction, and adynamic ileus all present together in a single case. Of these various forms, one usually predominates, and attracts surgical attention before the other forms have time to exercise their full pathologic effect. In rapidity of effect, strangulation takes precedence over closed loop obstruction, closed loop obstruction over simple occlusion of the lumen, and high occlusion over low occlusion.

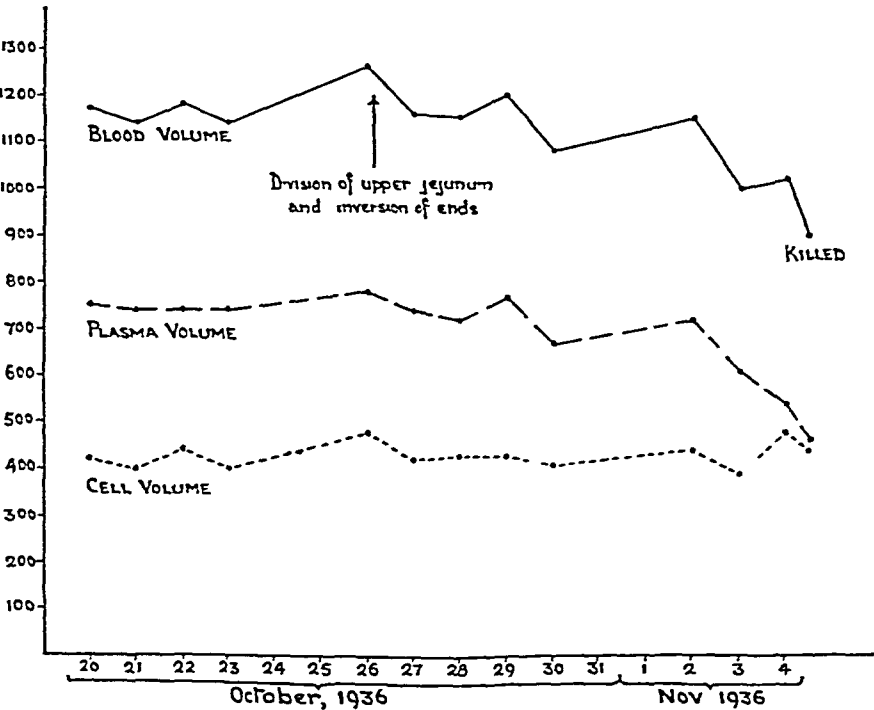
CLASSIFICATION OF TYPES OF OBSTRUCTION

- A Simple Occlusion of the Lumen
 - (1) High occlusion of the small intestine
 - (2) Low occlusion of the small intestine
 - (3) Colonic occlusion
- B Closed Loop Obstruction
 - (1) Sterile loops
 - (2) Heavily infected loops
 - (3) Mildly infected loops
- C Strangulation
 - (1) Short loops
 - (2) Medium loops
 - (3) Long loops

A SIMPLE OCCLUSION

(1) *High Small Intestine Occlusion*—High small intestine occlusion is the one form of intestinal obstruction in which experimental and clinical study has been completed. In consequence of the work of Maury, Hartwell and Hoguet, Haden and Orr, Elman and Hartmann, Armour, Jenkins, Wangen-

steen, and a host of other workers it is now recognized that all the phenomena of high small intestine obstruction are dependent upon the loss to the organism of water and of inorganic ions which, poured into the stomach and duodenum in enormous quantities as digestive juice fail to pass beyond the obstruction to be reabsorbed, as they normally are by the intestine below. The progressive loss of water leads to an increasing dehydration which is manifest clinically in the dryness of the patient's skin, the increasing thirst, and the diminution in urinary output. The blood becomes increasingly concentrated, the red cell count and the hemoglobin rise, and there is an increase in blood viscosity and sedimentation rate.



CHAPT 1—Showing the terminal depletion of blood volume in an animal subjected to high small intestine occlusion. The reduction in blood volume is wholly due to a fall in plasma volume, the result of dehydration. (By permission of the British Journal of Surgery.)

TABLE I

DOGS SUBJECTED TO HIGH SMALL INTESTINE OCCLUSION

The terminal reduction in blood volume is in each case due to a loss of plasma. (By permission of the British Journal of Surgery.)

No of Expts	Level of Occlusion	Duration of Life	Mean Blood Volume (Cc)	Reduction in Blood Volume (Per Cent)	Reduction in Plasma Volume (Per Cent)	Reduction in Cell Volume (Per Cent)
1	Terminal duodenum	5 days	1,030	25	43	—
2	Below ampulla	11 days	1,160	14	33	—
3	Below ampulla	6 days	1,360	23	44	7
4	Terminal duodenum	13 days	1,400	30	47	—
5	Terminal duodenum	9 days	1,180	44	32	—
6	Below ampulla	17 days	1,400	18	31	—

These striking effects of high small intestine occlusion may even alter the blood volume, and they alter it in a very characteristic way. Just before death, there is a remarkable reduction (Chart 1) in the volume of circulating blood. If Table I is studied, it will be seen that the terminal declension of the whole blood volume of dogs subjected to occlusion of the duodenum or upper jejunum is determined wholly by a reduction of the volume of the plasma, and that the volume of the red cells remains unaltered. It is profitable to compare this table with the blood volume tables of low small intestine obstruction and of strangulation (Tables IV and VII).

Dehydration is accompanied by demineralization. The chloride content of the blood and tissue fluid falls, and chlorides virtually disappear from the urine. In an attempt to maintain the total electrolyte content of the blood bicarbonate is withheld in the circulation, the bicarbonate content of the blood is demonstrably elevated, and the carbon dioxide combining-power is increased. Alkalemia is thus established. Meanwhile, as a direct result of the general dehydration, there is an increase in protein catabolism, and, before death, an elevation of the nonprotein nitrogen of the blood. The whole morbid sequence, dehydration, demineralization, alkalemia, azotemia, is too familiar to require further elaboration here, and is fully proved by a mass of clinical and experimental observation.

It is in the treatment of high small intestine occlusion (and in a less degree this applies to pyloric occlusion) that duodenal drainage and the intravenous saline drip have their most dramatic effect. In clinical practice, high small intestine occlusion in its purest form is seen in such conditions as postgastrojejunostomy vomiting, when a loop of jejunum running to or from the stoma becomes kinked, and all the duodenal juices are vomited, or in obstruction of the upper jejunum by bands or adhesions in the upper part of the root of the mesentery. Rarer varieties of obstruction at this level are duodenal ileus, volvulus neonatorum, congenital atresia of the duodenum or duodenojejunal junction, and herniation into the paraduodenal fossae or lesser sac in the upper abdomen.

Most high obstructions are due to simple occlusion of the lumen, and only occasionally does one of the upper loops of small intestine become strangulated. It must, however, be remembered that there are no clinical features to distinguish high occlusion from internal strangulation of one of the upper loops of jejunum. In cases of high intestinal obstruction, there is always a possibility that the obstructed loop is a strangulated loop. In consequence, unless the cause of obstruction is definitely known, and unless strangulation can be definitely excluded, it is unwise to continue duodenal drainage and intravenous saline infusion over too long a period, the restoration of water and chloride should be rapid, for strangulation may be present, and the need for operation is then urgent.

(2) *Low Small Intestine Occlusion*—This form of obstruction, the commonest clinical variety, has proved a complex problem for both the experimentalist and for the clinician, and it is safe to say that the precise cause of

death is not known. There are a number of factors probably responsible for the deterioration in the patient's condition in most cases, and it is possible that the predominant cause of death may vary from case to case. Most of the available data concerning intestinal obstruction have been obtained from the experimental animal. It should be remembered, however, that the cause of death of an animal suffering from untreated obstruction is not necessarily the same as the cause of death of a patient whose obstruction has been relieved by operation. Our patients suffering from acute obstruction are now invariably treated by operation, and deaths from acute intestinal obstruction now are postoperative deaths. We, of this generation, have virtually no experience of low small intestine obstruction untreated by operation, and our only knowledge of the full, fatal course of the untreated disease is obtained from animal experiment.

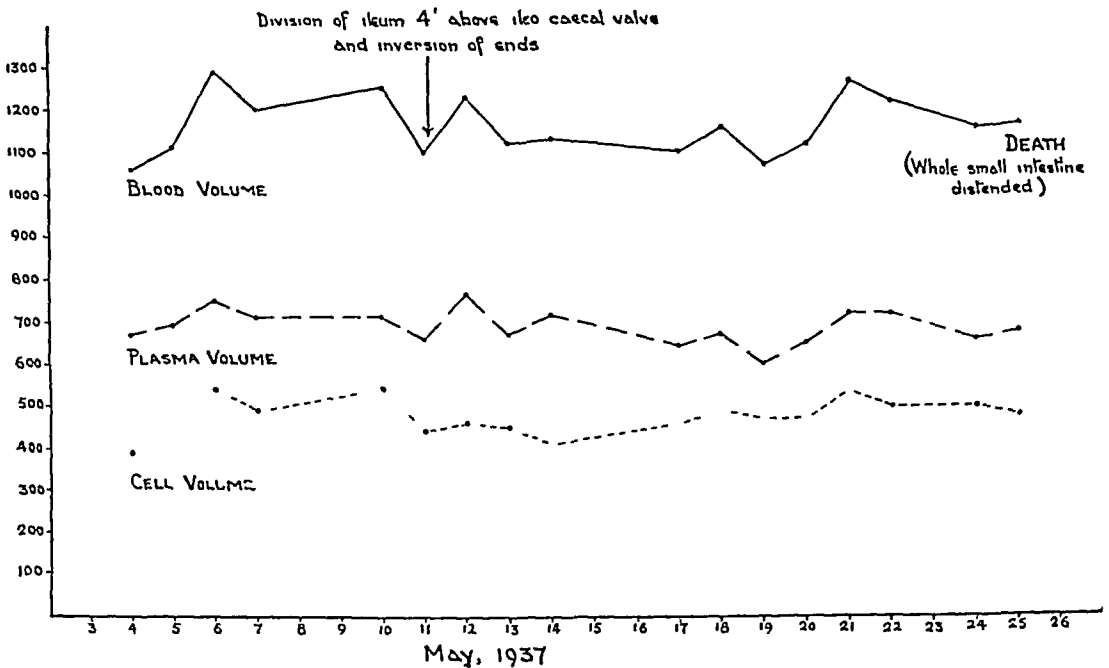


CHART 2—Low small intestine occlusion in the dog. Showing no reduction in blood volume, plasma volume, or cell volume at the time of death. (By permission of the British Journal of Surgery.)

During the last century, before operative relief became the standard treatment of acute intestinal obstruction, the patient suffering from acute, low small intestine occlusion died, as a rule, toward the end of the third, or during the fourth week of his illness. The duration of life then was the same as it is in the untreated experimental animal to-day. Even the patient suffering from internal strangulation lived into the second or third week after the appearance of symptoms. To-day, the sufferer from low obstruction comes under the surgeon's care after a few days or at most, a week of illness, his obstruction is relieved, and, if he dies, he dies within 24 to 48 hours postoperative. Fatal cases die sooner after the onset of obstruction to-day than they did a century ago.

The treated and the untreated cases of intestinal obstruction present sep-

arate problems, and require separate methods of study. The cause of death in unrelieved cases will be discussed first, and the cause of death in the case which is submitted to operation will be considered subsequently.

I Unrelieved Small Intestine Occlusion—The animal or man suffering from untreated low small intestine occlusion lives for a period of three or four weeks, during which a number of separate factors combine to produce a gradual deterioration in his general condition and vitality. Each of these morbid factors will be dealt with in turn.

Salt and Water Loss—In obstruction of the lower ileum, the loss of water and chlorides, while perhaps important in many cases, cannot be held wholly responsible for death. Even in the late stages of the disease, dehydration is often relatively slight (Chart 2), and it is rare to find a reduction of more than 25 per cent in the blood chlorides. In occlusion at higher levels, where chloride loss is the main or sole cause of death, the blood chlorides often reach an agonal level of 50 per cent. Many cases of low small intestine obstruction—the majority of them in my experience—die with no great alteration in the chloride content of the blood, without a high degree of alkalemia, and with little, if any, elevation in the nonprotein nitrogen of the blood. In some cases, no change whatever is demonstrable in the blood chemistry.

Certain cases of low small intestine occlusion do, of course, present a considerable water and salt loss. Vomiting is relatively late, but, above the obstruction, intestinal juices accumulate in the loops of bowel, and distend them so that the veins in the bowel wall are congested, the mucosa becomes edematous, and there is a progressive increase in the secretion of juice from the intestinal glands. Water and electrolytes, accumulating in the lumen of the bowel, are lost to the organism just as surely as if they were immediately vomited. In such cases as these, dehydration and chloride depletion require treatment, and they perhaps play some part in the so-called "toxemia" of obstruction. Yet administration of water and chlorides does not greatly prolong the life of a man or of an animal suffering from unrelieved simple occlusion of the lower ileum.

The duodenal tube, too, invaluable in high intestinal occlusion, has some application in the treatment of low occlusion. Through a nasal suction tube, the duodenal juices may be withdrawn, and may so be prevented from descending into the distended lower loops of bowel and adding to the stagnant intestinal content. The most distended loops of bowel, however, are those which lie immediately above the obstructing agent, and it is difficult, in most cases, to decompress these lower loops satisfactorily by way of a duodenal tube. These lower distended loops appear to be in themselves mainly responsible for the so-called "toxemia" of low small intestine occlusion, and their distention may cause death long before the loss of fluid and salt into them has given rise to any degree of dehydration or hypochloremia. The cause of death in low small intestine obstruction must be sought in the distended bowel loops.

Perforation and Peritonitis—In the experimental animal, the course of a

low small intestine occlusion is frequently terminated by a perforation of the distended bowel, and peritonitis. This cause of death is not commonly seen now in man, since the patient comes to operation, in the vast majority of cases, before perforation occurs. Reference to any text-book of surgery written during the last century will convince the reader that perforation of the ileum from a stercoral ulcer was relatively common as a terminal event in unrelieved low small intestine occlusion then, just as it is to-day in the experimental animal.³²

Reflex Nervous Causes—It has been contended that reflex depression of the circulation by sensory impulses from the distended bowel plays an important part in low intestinal obstruction, but until recently there has been little evidence in favor of this theory. Herrin and Meek¹⁸ succeeded in establishing a distention of bowel without any occlusion of the gastro-intestinal lumen. They isolated a bowel loop and reconstituted the lumen of the intestine around it. The isolated loop was then anastomosed to the reconstituted bowel on the one hand, and brought out on the skin surface on the other. (The fistula produced in this way is known as a Thiry-Vella fistula.) Into this isolated loop a balloon was inserted and inflated. The balloon distended that part of the loop in which it lay, but the bowel on each side of the balloon drained satisfactorily, either into the main intestinal canal or on to the skin surface. Balloon distention of this kind was found by Herrin and Meek to be rapidly fatal, producing a serious diminution of the blood chlorides and elevation of the nonprotein nitrogen. This effect of distention on the blood chemistry Herrin and Meek believe to be due to a reflex hypersecretion of intestinal juice. Denervation of the distended loop permitted the animal to live almost indefinitely. These experiments were repeated by Taylor, Welch, and Harrison,³¹ who confirmed the fatal effect of balloon distention of a Thiry-Vella loop, but were not successful in prolonging life by denervation of the distended bowel.

In several experiments, I have maintained balloon distention of Thiry-Vella fistula loops, and have not found that distention, in itself, is necessarily fatal. In one animal, a balloon inserted into a Thiry-Vella loop was maintained at a high state of tension by repeated inflation, yet the animal continued to live, without serious symptoms, for 35 days, when it was sacrificed. During this whole period, the balloon within the fistulous loop was palpable as an abdominal tumor, yet no serious symptoms arose. This single experiment is almost sufficient in itself to suggest that afferent impulses from the obstructed bowel have little, if anything to do with the so-called "toxemia" of low obstruction.

Splanchnic Congestion—Loss of blood and plasma into the wall of the distended, congested bowel above a simple occlusion has been said to occasion a depletion of the circulating blood volume, and has been blamed for death in cases of low occlusion. The evidence upon which this theory rests is to be found only in groups of experiments in which the wall of obstructed bowel is weighed, and the amount of fluid and blood lying in it estimated. Actually,

even by this method, when the distended portion of the intestine above the occlusion is compared in weight with collapsed bowel below, the gain in weight of the distended loop from the blood in its congested vessels and the plasma in its edematous wall is relatively small when expressed as a percentage of the blood volume

TABLE II

LOSS OF EFFECTIVE CIRCULATING BLOOD VOLUME IN SIMPLE LOW SMALL
INTESTINE OCCLUSION

Degree of splanchnic congestion measured by a comparison of the weights of loops of equal length taken from above and from below the occlusion after death (By permission of the Edinburgh Medical Journal)

	Fraction of Intestine Isolated as Closed Loop	Dura- tion of Life	Weight of Closed Loop (Gm)	Weight of Healthy Loop of Equal Length (Gm)	Gain in Weight of Closed Loop (Gm)	Weight of Animal (Gm)	Blood Volume (approx) (Cc)	Loss of Edema Fluid and Blood Expressed as Percentage of Blood Volume
1	One-half	2 days	48 0	23 0	25 0	3,100	233	11 0
2	One-quarter	6 days	14 3	9 8	4 5	2 900	218	1 6
3	One-fifth	4 days	13 3	10 9	2 4	2,600	195	1 3
4	One fifth	4 days	11 1	7 8	3 5	2,400	180	1 8
5	One-fifth	3 days	10 9	7 4	3 5	1,900	143	2 5
6	One-seventh	4 days	11 7	7 0	4 7	2,400	185	3 0
7	One tenth	5 days	12 3	8 4	3 9	2,700	203	1 9

TABLE III

LOOPS OF SMALL INTESTINE OF CATS ISOLATED BY DOUBLE LIGATION AND INVAGINATION AND
PERMITTED TO DISTEND AS CLOSED LOOPS

Lengths of bowel equal in length to the closed loops were marked off at the time of establishment of the obstruction by seromuscular stitches of silk, and after the death of the animal were compared in weight with the closed loops. A simple occlusion of the lumen was avoided in these animals by short-circuiting the small intestine around the closed loop

	Fraction of Small Intestine Distended	Weight of Distended Loop (Gm)	Weight of Healthy Loop of Equal Length (Gm)	Weight of Plasma and Blood Lost into Bowel Wall (Gm)	Estimated Blood Volume (Cc)	Blood and Plasma Ex- cess in Bowel Wall Expressed as Percentage of Blood Volume
1	One-half	105 0	24 0	81	233	34
2	One-half	85 0	21 0	64	172	37
3	One-quarter	47 4	11 4	36	210	17
4	One quarter	41 0	14 0	27	225	12
5	One-eighth	23 5	8 5	15	165	10

In Table II, it will be seen that if an occlusion is established in the middle of the small intestine, the sum of edema-fluid and blood lost into the upper distended half above the obstruction amounts to only 11 per cent of the blood volume. The whole length of small intestine similarly distended would pre-

sumably accommodate a volume of edema-fluid and blood equivalent to little over 20 per cent of the blood volume. Even if this loss were of whole blood, it would be comparable with the blood lost in a considerable, but certainly not in a serious, hemorrhage. The theory of splanchnic congestion, however, has gained so much support, and the measurement of blood lost by the weighing of distended bowel loops is admittedly so inaccurate, that it was felt necessary to estimate directly the effect of splanchnic congestion on the blood volume. In a series of animals, the blood volume was measured on several occasions before the establishment of low occlusion, and at repeated intervals in the survival period after the operation had been performed. Illustrative results are shown in Table IV. Most of the animals died with no alteration whatever in the volume of the whole blood or plasma, and even when death was obviously impending there was no such reduction in blood volume as occurs in extensive strangulation, for example, or in high small intestine obstruction. For this reason, I believe that the loss of blood and plasma into the congested and edematous wall of the obstructed bowel is not the main cause of death in low small intestine occlusion.

TABLE IV

ILLUSTRATIVE DATA FROM DOGS SUBJECTED TO LOW SMALL INTESTINE OCCLUSION

In Dogs Nos. 1 and 4 death has occurred with no reduction whatever in blood volume. In Dogs Nos. 2 and 3 there is a considerable reduction in blood volume, in plasma volume, and in cell volume. In these animals, the small intestine was distended to the point of nonviability—a degree of distention-congestion rarely seen in man. (By permission of the British Journal of Surgery)

No of Exper	Level of Occlusion	Dura- tion of Life	Mean Blood Volume (Cc)	Reduction in Blood Volume (Per Cent)	Reduction in Plasma Volume (Per Cent)	Reduction in Cell Volume (Per Cent)
1	Lower ileum	14 days	1,170	—	—	—
2	Lower ileum	7 days	2,020	23	31	20
3	Lower ileum	9 days	1,610	44	50	37
4	Lower ileum	9 days	1,410	—	—	—

It is necessary to add, however, that in a certain proportion of animals the blood volume is to some extent depleted before death and that the depletion affects both plasma volume and cell volume. This occurs only when intestinal distention is extreme, and when the congestion of the bowel wall is so great above the obstruction as to suggest incipient devitalization. Such a marked engorgement of obstructed intestine, frequently seen in the laboratory animal suffering from intestinal occlusion, does not commonly occur now in man. In the untreated case before the days of modern surgery, however, it would appear from the literature that gross congestion of the bowel was common at the time of death, and a considerable blood loss may have been present in these cases, just as it now is sometimes in the experimental animal.

Potassium Poisoning—Scudder and his coworkers²⁹ have blamed potassium poisoning for the lethal effects of intestinal obstruction. They have shown that in a certain number of cases the potassium content of the blood is

elevated both in clinical and in experimental cases of intestinal occlusion Scudder suggests that the elevation of blood potassium is associated with adirenal insufficiency, and recalls that Wohl *et al*,³⁷ examining the adrenal glands in obstructed animals, found a depletion of the cells of the cortex It should be observed, however, that in only seven out of 20 of Scudder's cases was the plasma potassium elevated, and in only five instances was the blood potassium raised Elevation of potassium, therefore, does not seem to be an essential factor in intestinal obstruction Scudder found the blood potassium more altered in cases of high occlusion than in cases of low occlusion, and it is noteworthy that Wohl *et al* observed cortical depletion only in those dogs suffering from intestinal obstruction which were not treated by saline Saline treatment seems to prevent adirenocortical depletion It seems possible, therefore, that the alteration in the adrenal glands and in the potassium metabolism may be a function of chloride loss

It has been shown that adirenocortical extract may be given with benefit in cases of intestinal obstruction, but this is in itself no proof of adirenal deficiency The beneficent effect of cortical extract may be due purely to the mobilization of chloride which it occasions It certainly appears to be most effective in cases of high small intestine obstruction where the blood chloride is low

Toxemia—From time to time various toxic theories have been elaborated to explain the lethal effects of intestinal obstruction, the most recent proponent of the toxemia theory being M J Bottin,¹² of Liege, who suggests a toxemia of pancreatic origin to explain not only ileal obstruction, but high small intestine obstruction as well It has never, however, been shown by injection methods that any toxins circulate in the blood of men or of animals suffering from intestinal obstruction, nor, indeed, is this theory of toxemia supported by cross-circulation experiments This negative statement is no proof, of course, that toxemia does not occur In an animal suffering from such a definite toxemia as diphtheria or strychnine poisoning, for example, it is difficult to prove, by injecting that animal's blood into another animal of the same size, that the blood has toxic properties The apparent absence of toxic properties from small quantities, or even large quantities, of blood is no evidence of the absence of toxemia

There is, however, one important argument against the presence of a toxemia in the patient, or animal, who suffers from intestinal obstruction That argument is that all absorption is retarded in distended bowel loops There is no question that many chemical and bacterial toxins are present in the lumen of an obstructed bowel, just as they are present in the lumen of a normal bowel, but in neither case does absorption of that toxic material appear to occur

Let me recall an important classic experiment of Braun and Boruttau which demonstrates how much absorption is lessened in a distended bowel loop If, in an experimental animal, a bowel loop is isolated and distended with saline until congestion occurs in the wall of the loop, a fatal dose of strychnine injected into the lumen of the distended loop does not produce any

symptoms of strychnine poisoning. The strychnine has failed to pass from the lumen of the distended loop into the blood stream. A similar retardation of absorption has been shown for electrolytes and for certain dyes^{11, 13, 22}. So, in intestinal obstruction, it seems unlikely that there is a passage of toxin from the lumen of the distended bowel to the blood stream.

It might be argued that, though direct absorption from the lumen of the bowel to the blood stream is delayed in the presence of intestinal distention, lymphatic absorption from the distended bowel is accelerated by the congestion which occurs in its wall. Wangensteen³⁴ has shown experimentally, however, that ligation or division of the lymphatic pedicle draining a distended bowel loop does nothing to prolong life.

Starvation and Alimentary Depletion—This factor in the morbidity of intestinal obstruction has received insufficient attention. The patient who presents nowadays with low small intestine occlusion has been ill for only a few days, as a rule, and a few days' starvation cannot be responsible then for a fatal issue, though it should be remembered that even a day or two of starvation exaggerates the general effect of any form of trauma or disease. Previously, however, when the patient lived untreated for three weeks or more after the onset of obstruction, starvation must have been an important factor, just as it is, no doubt, in the experimental animal suffering from low small intestine occlusion to-day. In the presence of acute obstruction, the patient or animal, as a rule, refuses food, but even if food materials are ingested they are not absorbed. The intestine above the obstruction is distended, circulation is enormously slowed in the bowel wall, and the main function of the intestine, that of absorption, has come to a standstill. Not only the water and chloride content of the intestinal juice, but the products of digestion, the cholalic acid, the glycine and the taurine of the bile salts, the lipoids (cholesterol and lecithin) of the bile, failed to reach the circulation. The steady loss of these substances over a period of two or three weeks amounts to a serious alimentary depletion.

We have attempted, in the experimental animal, to overcome the factor of alimentary depletion by the intravenous administration of chyle. B. M. Dick¹⁵ first suggested that chyle might prove a suitable food material for intravenous injection in marasmus and other forms of cachexia, and his suggestion has been applied to the treatment of dogs suffering from intestinal obstruction. Large quantities of chyle were collected, and were injected intravenously into obstructed animals.

Technic of Collection of Chyle for Intravenous Administration to an Obstructed Animal—The difficulty in these experiments was to obtain a sufficient quantity of sterile chyle. It was considered that, by the production of chylothorax in healthy animals, reservoirs of chyle might be obtained, to be tapped at convenient times by paracentesis thoracis. Chylothorax, however, is difficult to produce experimentally. Mouchet²⁵ succeeded in obtaining chylothorax only twice in a long series of animals, by the establishment of a simple fistula between thoracic duct and pleural cavity, and even in these two cases the chylothorax was transitory.

In our earlier experiments, it was found that if the thoracic duct is merely

divided and its lower end transplanted into the pleural cavity, the communication between duct and pleura rapidly closes. Apparently, after division of the thoracic duct, other anastomotic lymphatic channels open, and a new route is established for the passage of chyle from the abdomen to the great veins of the neck. It was felt that, in addition to an anastomosis between thoracic duct and pleura, some means must be found of preventing chyle from reaching the great veins by alternative routes. The simplest method of interfering with the drainage of chyle into the veins of the neck appeared to be by the ligation of the superior vena cava. Ligation of the left innominate vein did not suffice to produce an actual stasis, since, in the dog at least, there appears to be a subsidiary route for chyle by way of the right lymph duct to the right innominate vein. The following method was, therefore, elaborated. The right pleural cavity was opened, and the thoracic duct identified in the lower mediastinum. The mediastinal pleura was then torn through with an aneurysm needle, and the thoracic duct cut across. The superior vena cava was then ligated in the upper part of the mediastinum, and the vena azygos was also ligated toward its termination. After this operation, a chylothorax developed on the right side in nearly every case. The pleural cavity was tapped daily after the operation. On the first few occasions, a thin, blood stained fluid was withdrawn, but, later, white, milky chyle was obtained. Sometimes as much as 500 cc of chyle was obtained daily from the larger dogs. The chyle obtained in this way clotted soon after withdrawal if left at room temperature, and the addition of citrate did not, of course, prevent coagulation. It was found, however, that if the chyle was placed in a refrigerator immediately after withdrawal, coagulation was largely avoided. Our routine practice, therefore, was either to inject the chyle obtained immediately, or, better, to leave the chyle at a refrigerator temperature of 1° or 2° F for a day or two. Before injection, any coagulum was removed by filtration.

In this way, a constant reservoir of chyle was available. A number of animals were subjected to low small intestine occlusion, and were treated by the daily intravenous injection of chyle. It was found that in no case did the chyle exercise an obvious toxic effect. The average daily dose of chyle was arbitrarily fixed at 30 per cent of the estimated blood volume of the recipient dog. Five dogs were treated in this way. One of these died after a period of ten days. Two other dogs lived for a period of three weeks. One dog lived until the thirty-first day, and in the fifth animal, death was postponed till the thirty-fifth day. All five animals died of perforation of the small intestine, and peritonitis. The statistics in this series are not, of course, conclusive, suggestive as they are, they are best left without comment. They perhaps indicate, however, that the transfusion of chyle as a treatment of alimentary depletion and starvation might prove a fruitful field for investigation.

II *The Cause of Death in Cases of Low Small Intestine Occlusion after Operative Relief of the Obstruction*—It has already been mentioned that no definite toxemia has ever been proved to be present during the actual presence of an abdominal distention or obstruction. There is, however, some evidence

that a toxemia may result from the sudden deflation of distended bowel loops. We are all familiar with the clinical case of intestinal obstruction in which the patient is admitted to hospital relatively early in the disease, with a considerable abdominal distention, but yet in a fairly good general condition. Operation is performed, and the obstruction is successfully relieved. After operation, the abdomen loses its distention to some extent, yet the patient gradually sinks into a listless apathy, the pulse rate rises, the blood pressure falls, and in an hour or two, or in a day or two, the patient dies. The patients who die from intestinal obstruction nowadays die, as a rule, after an operation has been performed.

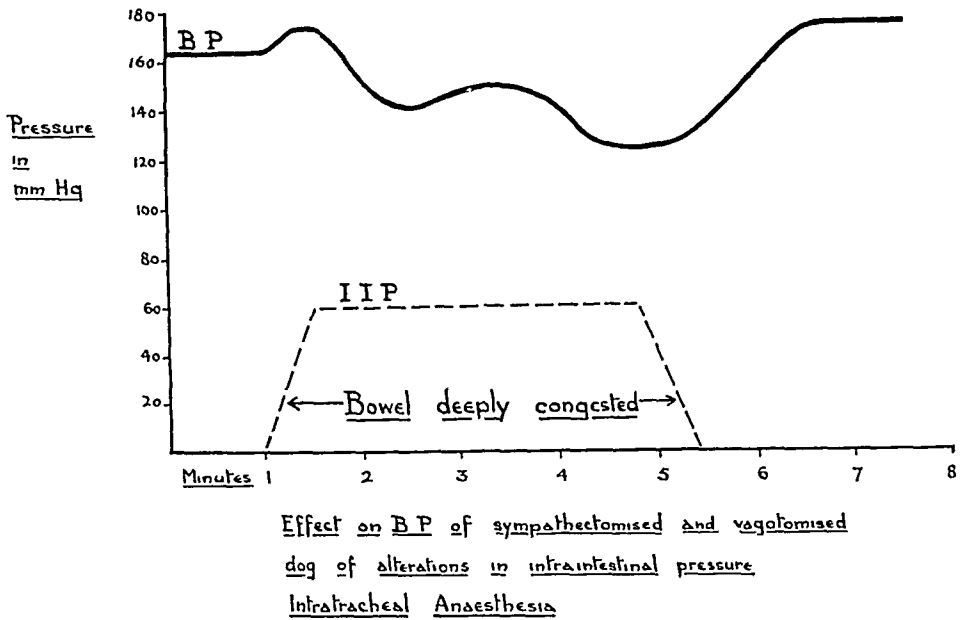


CHART 3—Demonstrating that induction of distention and congestion of small intestine causes a fall in systolic pressure, apparently the result of splanchnic congestion. Relief of distention and congestion after a few minutes is followed by elevation of systolic pressure, as a result of the return of blood from the congested bowel to the general circulation (Cf Charts 4, 5 and 6)

The same phenomenon is seen clinically in an even more extreme degree in cases where a strangulation is relieved by operation, and it is seen in its most characteristic form after reduction of an intussusception. There are cases of intussusception in which, at operation, the intussusception is reduced, and the intussusceptum, obviously still viable, is returned to the abdomen, after operation, within 24 hours, as a rule, the temperature and the pulse rate rise, the systolic blood pressure falls, the patient becomes pale, sometimes listless, sometimes excited, and death may occur. This alarming phenomenon sometimes happens rapidly, and it may even occur on the operating table. It is notorious that the postoperative course of an intussusception is likely to be more serious if the invagination is difficult to reduce, and if the intussusceptum has to be forcibly squeezed out from its sheath by a long-continued manipulation.

The rapid and lethal depression of the systolic blood pressure which may

follow relief of an intestinal obstruction was seen with greater frequency in former times, when attempts were made by aspiration of distended bowel loops to empty these loops rapidly at operation, and when it was customary to milk down distended bowel at operation, to evacuate it. Let us examine whether the postoperative deaths in intestinal obstruction are due simply to the

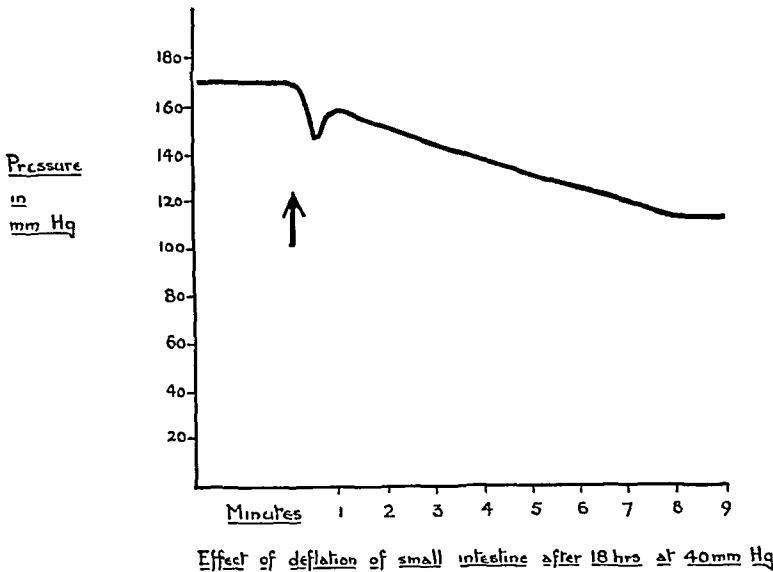


CHART 4

CHARTS 4, 5 and 6—Demonstrating that release of a long continued distention, congestion of bowel in the dog is followed by a serious and some times fatal depression of the systolic pressure

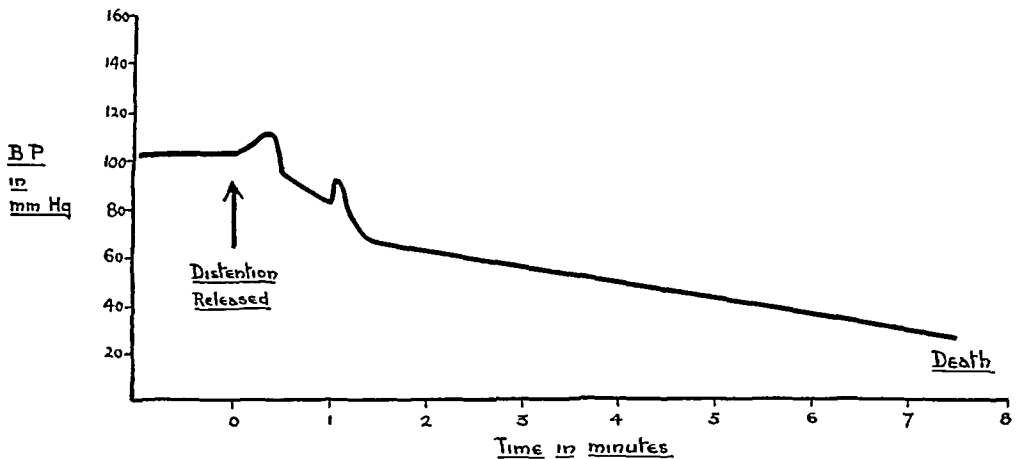


CHART 5

shock of an abdominal operation performed upon a seriously ill patient, or whether there is a specific depressor factor in the actual release of obstruction

It has been possible, experimentally, to produce a depressor effect in ani-

mals by the sudden relief of intestinal distention^{2 3 4} If the whole small intestine of an animal is rapidly inflated to the point of cyanosis, there is a sudden depression of the systolic blood pressure This appears to be due to the loss of effective circulating blood into the distended vessels of the inflated bowel, and is an effect of splanchnic congestion, after its initial depression, the blood pressure usually rises again quite rapidly to normal If the distended bowel is suddenly collapsed soon after its inflation, its congestion quickly disappears, its engorged veins empty, there is an increased blood return to the heart, an augmentation of the circulating blood volume, and a transient rise in blood pressure (Chart 3) If, however, the intestinal distention is maintained for a long period, and is then rapidly released, there occurs, not an elevation, but a depression of the blood pressure (Charts 4, 5, 6 and Table V)

TABLE V

EXPERIMENTS SHOWING EFFECT OF RELEASE OF DISTENTION-CONGESTION OF BOWEL

Early relief leads to increased return of venous blood from congested bowel to heart Systolic pressure rises (protocols Nos 1 to 9) The delayed relief of long-continued distention-congestion is followed by improvement in color of bowel, presumably by increased blood return to the heart, but by a depression instead of an elevation of the systolic pressure This suggests the return of a depressor substance to the general circulation from the previously obstructed intestine (Experiments Nos 10 to 14)

No of Expt	Intra-intestinal Pressure Induced	Animal	Afferent Paths from Heart Interrupted	Afferent Paths from Intestine Interrupted	Duration of Distention	Change in Bowel Circulation (color)	Alteration in B P	Explanation
1	62 Mm Hg	Dog	Yes	No	5 min	Return from cyanosis to normal	+ 28	
2	80 "	Cat	Yes	No	5 min	"	+ 50	Increased
3	90 "	Dog	Yes	Yes	2 min	"	+ 30	
4	90 "	Cat	Yes	Yes	5 min	"	+102	return of
5	100 "	Dog	Yes	Yes	4 hrs	"	+ 28	
6	120 "	Dog	Yes	Yes	8 hrs	"	+ 44	venous
7	90 "	Dog	Yes	Yes	7 hrs	"	+ 22	
8	80 "	Cat	Yes	Yes	5 hrs	"	+ 68	blood to
9	Release of ligation of superior mesenteric vein of dog					"	+ 24	heart
10	90 Mm Hg	Dog	Yes	Yes	6 hrs	Return from cyanosis to normal	- 55	? Return of depressor substance
11	90 "	Dog	Yes	Yes	17 hrs	"	- 78 (death)	in blood from intestine
12	90 "	Dog	Yes	Yes	18 hrs	"	- 32	
13	40 "	Dog	Yes	Yes	12 hrs	"	- 56	
14	80 "	Dog	No	No	12 hrs	"	- 23	
15	90 "	Dog	Yes	Yes	21 hrs	Remained cyanosed	No change	Thrombosis in bowel veins
16	90 "	Dog	Yes	Yes	17 hrs	"	"	

The fall in blood pressure in these animals occurred even after the complete denervation of the bowel, either by division of the mesenteric nerves or by bilateral excision of the sympathetic trunk and double vagotomy. When the distended intestine is deflated, the distended intestinal veins empty, blood returns from these veins to the general circulation and augments the blood volume, and yet, instead of a rise of blood pressure, there is a fall, which is sometimes progressive over a period of some hours, and which is occasionally fatal. This fall in blood pressure would appear to be due to the passage of toxic depressor material into the blood stream. Toxic material from the lumen has, during distention, diffused into the tissue fluids of the bowel wall, but has failed to enter the blood stream, because of the intestinal congestion which is

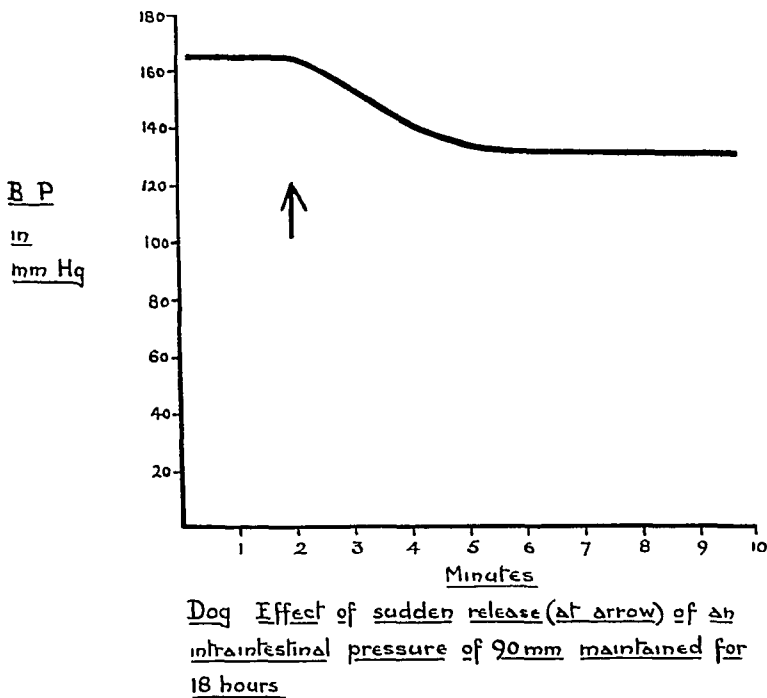


CHART 6

present. On the relief of congestion, the tissue fluid, bearing the toxic material which it has acquired during distention, enters the intestinal capillaries and returns with the intestinal blood to the general circulation, to exercise a depressor effect.

Braun and Borittau recorded an ingenious and dramatic experiment which is of some value in this connection. As I have already mentioned above, Braun and Borittau found that a lethal dose of strychnine could be injected into an isolated and distended bowel loop in the experimental animal without the appearance of symptoms, provided the intra-intestinal pressure was sufficiently high in the isolated loop. They showed, however, that sudden deflation of the strychnine-containing loop was followed, as a rule, by the immediate appearance of strychnine convulsions, and by the early death of the animal. The effects of sudden deflation of a distended loop containing strychnine were

almost as rapid as the effects of intravenous injection of the drug. Braun and Boruttau explain these experiments in this way. They consider that, during distention, the strychnine passes into the stagnant tissue fluid of the congested wall of the distended bowel, but fails to pass into the blood stream, because of the sluggishness of local circulation in the bowel. As soon as the distention and congestion of the bowel loop are relieved, however, the local circulation recovers, and strychnine is able now to diffuse rapidly from the tissue spaces into the blood stream. It appears likely that, in intestinal obstruction, toxic material from the lumen behaves in the same way. During distention it passes into the tissue spaces of the bowel wall, but succeeds in reaching the blood stream only when the local circulation in the bowel is improved by deflation.

The nature of the toxin which produces a depressor, and sometimes a lethal, effect on the experimental animal after the relief of an obstruction is not known. Blood collected from the portal vein and from the mesenteric veins during deflation of a distended bowel loop has been shown to have sometimes a depressor effect when injected into other animals.⁴ It can thus be fairly argued that, while no proof has ever been offered of a true toxemia during intestinal distention, there is considerable evidence that a rapid toxemia may occur soon after the relief of intestinal distention.

One important principle emerges—the immediate relief of an early obstruction is beneficial—a low blood pressure will rise. Sudden release of a long-continued distention of the bowel, with severe intestinal cyanosis, is likely to be followed by a perhaps dangerous fall in blood pressure, and some part of the present (postoperative) mortality of obstruction may be explained by the depressor effect of sudden relief of intestinal distention-congestion.

The results of sudden intestinal deflation are an important argument against aspiration of distended bowel loops at operation, and the milking down of distended bowel to empty it forcibly. Storck and Ochsner³⁰ have demonstrated how serious a depressor effect such mechanical decompression of the intestine may have on the carotid blood pressure in the experimental animal.

The depressor effect of deflation in the experimental animal may suggest that any form of relief of a long-continued obstruction may not be without danger. The risk of sudden decompression of distended bowel has been particularly stressed by Wheeler,³⁵ who points out that wherever fluid is present under tension in the body a sudden evacuation of the fluid may have a serious effect. Wheeler advocates that distended bowel in obstruction be decompressed as slowly as the pleural cavity in empyema, or the distended bladder in retention of urine. Our experiments in deflation of bowel strongly support Wheeler's contention. The surgeon who accepts the validity of our argument is on the horns of a dilemma when faced with an acute intestinal obstruction of long standing. On the one hand, he cannot permit obstruction to continue, and on the other, he is aware of the possible risk of sudden release of the obstruction. Time alone will produce a satisfactory solution of this problem. In the meantime, the experiments described strongly support recent suggestions for slow decompression of distended bowel, either by preoperative nasal

suction drainage, as suggested by Wangensteen,³⁴ or by some form of controlled enterostomy which permits the distending gas to escape, only gradually, over a period of some hours

Let it be understood, finally, that this demonstration of a toxemia which follows upon the sudden relief of a long-continued intestinal distention can be applied only to the postoperative toxemia of acute intestinal obstruction. There is no evidence that an actual toxemia is present during the presence of an unrelieved intestinal distention. It might be argued that, during distention, a sudden wave of peristalsis passing over the distended bowel might squeeze from it, into the circulation, some of the toxic products which appear to lie within its wall. Peristalsis may perhaps have the same effect during an obstruction as do milking and stripping of the bowel at the time of operation. A theory of an intermittent toxemia due to the entry into the circulation of toxic material from the bowel with each vigorous peristaltic wave must remain a matter of conjecture. The other morbid factors which have been shown to be present throughout the relatively long course of an untreated low small intestine obstruction are sufficient, however, to explain death, and there need be no resort to a hypothetic, intermittent toxemia in these cases.

(3) *Colonic Occlusion*—Colonic occlusion is particularly well tolerated in experimental animals, and dogs with a complete obstruction of the lower colon may live without symptoms for as long as a month. This is hardly comparable, however, with colonic occlusion as it occurs, typically, in man. The cause in man is usually cancer, and acute obstruction, when it supervenes, occurs only as the culmination of a long-continued, subacute obstruction, as a rule. The bowel has already been dilated, its muscle wall hypertrophied, and the mucosa not infrequently the seat of stercoial ulceration before obstruction becomes complete. Furthermore, the patient is frequently in poor general condition, and sometimes even cachectic. For this reason, colonic occlusion is a more serious form of obstruction in man than it is in the experimental animal. If the occlusion becomes complete, the intracolonic pressure rises to a high level, but the ileocecal sphincter remains competent until a late stage. Ultimately, in most untreated cases, the pressure rises to such a high level within the colon that perforation of its wall occurs, the perforation being situated, as a rule, in a stercoial ulcer of the cecum. In most cases of colonic occlusion, no significant alteration occurs in the blood chlorides, the blood volume, the bicarbonate content, or the blood urea.

B CLOSED LOOP OBSTRUCTION

Closed loop obstruction has specially lent itself to experimental study, and, as Wilkie first observed, the pathologic course of a closed intestinal loop depends upon the degree to which its contents are infected by bacteria.

(1) *Loops with Sterile Content*—The best examples of the sterile loop in man are mucocele of the appendix, cyst of the vitello-intestinal duct, and the various enterogenous cysts. As a rule, when a sterile loop of bowel is isolated from the intestinal tract, it dilates gradually with mucus, and no general effects

follow. In the experimental animal, an isolated bowel loop can be effectively sterilized, and, in most cases, after its ends are closed, it dilates, as a similar loop does in man—as a mucocele. In only a few cases does the loop distend so rapidly with mucus that vascular changes occur in its wall, and the animals die after three or four days (Taylor⁴¹).

(2) *Closed Loops with Heavily Infected Content*—Wilkie's³⁶ second form of closed loop obstruction is best seen clinically in obstructive appendicitis. Such a loop contains grossly infected fecal matter, and is closed at both its ends. The organisms within it multiply rapidly, gas accumulates in the lumen, the pressure within the loop rises rapidly, fluids and leukocytes are poured into the lumen, and a pyocele, or empyema, forms. Soon the increase in pressure interferes with the local circulation, organisms enter the devitalized bowel wall, and gangrene, perforation and peritonitis follow. Other things being equal, a small infected loop is more liable to early perforation than is a long one, perhaps because a small loop accommodates itself less easily to a rapid increase in the volume of its content, and more rapidly develops a high pressure within it.

(3) *Closed Loops with Mildly Infected Content*—Loops of this sort are seen between multiple strictures of the small intestine and in herniae which are obstructed but not yet strangulated. In the clinical case in man, a closed loop is always complicated by a simple bowel occlusion above it, but in the experimental animal closed loops can be prepared without a complicating occlusion. The closed loop is in that case short-circuited by anastomosis, and is sometimes employed in the study of the so-called "toxemia" of obstruction. The closed loop distends in the course of a few days with foul gas and with dark-brown, blood stained fluid, whose constituents include intestinal juice, leukocytes, fragments of dead epithelium, whole blood and bacteria. The intraloop tension reaches an enormous level, sometimes as high as 70 cm. of water, because the closed loop cannot relieve the pressure within it by evacuation of some part of its content upwards, as the distended bowel above a simple occlusion can. The intra-intestinal pressure within a closed loop rises more rapidly and to a higher level than does the pressure in the bowel loops above a simple occlusion. The walls of the loop are tense and congested and edematous, with bacterial invasion and leukocyte infiltration. The mucosa is necrotic and ulcerated, as a result of the high tension within the loop, and cyanosis is soon obvious in it. The muscle coat is flabby and inflamed, and the serosa is usually congested. The terminal changes in the bowel wall are sometimes very similar to the changes of strangulation.

A loop of this kind closely resembles the lowest distended loop above a simple low intestine occlusion, and it is difficult not to believe that the cause of death is similar in both these conditions. There are certain modifying factors, however, in the course of a closed loop. Perforation and peritonitis, while not necessarily present before death, are rather more frequent in the closed loops than in cases of simple occlusion. Where death occurs without perforation and peritonitis, the closed loop will usually be found in a state of gross conges-

tion, and reference to Table III will demonstrate that the blood and fluid lost into the wall of a long, closed loop may amount to as much as one-third of the total blood volume. So great, indeed, may be the congestion of the loop that at the time of death it may be considered to be in a state of strangulation, not from occlusion of its mesenteric vessels, but from closure of the vessels in the wall of the loop itself, as a result of the enormous intraloop pressure. The relatively common incidence of perforation and peritonitis, the increased degree of blood loss from the general circulation, and the occurrence of actual devitalization in the wall of the distended bowel are three factors which explain why the course of closed loop obstruction is so much more rapid than the course of simple occlusion of the bowel.

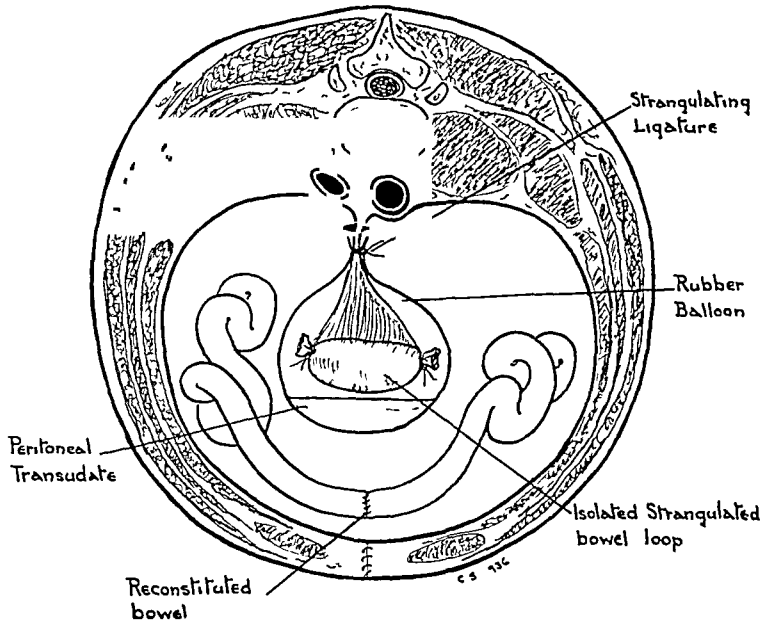


FIG. 1—Showing the method of determining blood loss following strangulation (Foster and Hausler). An isolated bowel loop is placed in a rubber bag and strangulated by a ligature tied around the neck of the bag. The intestinal lumen is reconstituted around the isolated loop by anastomosis.

It should be remembered that sudden deflation of a closed loop may exercise the same toxic effect as sudden relief of a simple occlusion or a strangulation.

C. INTESTINAL STRANGULATION

Pure forms of intestinal strangulation are rare clinically. In strangulation by hernia, for example, or by a band, a simple occlusion is present usually above the strangulated loop, but the effects of strangulation are so rapid, as compared with the effects of simple occlusion, that the strangulation element always outweighs in importance the occlusive element. Strangulation is seen in a pure form in mesenteric embolism and thrombosis.

It is convenient to consider strangulation under three heads, since the predominant lethal factor appears to vary according as a strangulated loop is very short, very long, or of medium size.

(1) *Short Loop Strangulation*—This form is exemplified clinically by the small, nonviable patch of bowel wall which, on occasion, may occur in a Richter's hernia, or at the apex of a reduced intussusception. It is also seen clinically in the late obstructed appendix when circulation has ceased in the vessels of the appendix wall. In strangulation of a short loop, death is due, as a rule, to gangrene, rupture and peritonitis.

(2) *Long Loop Strangulation*—Long loop strangulation is clinically exemplified by mesenteric thrombosis and embolism, and the picture of the patient suffering from occlusion of the superior mesenteric artery or vein is characteristic. The sudden pain at the onset of the disease is followed rapidly by a progressive pallor, increase in pulse rate, and fall in blood pressure. An enormous volume of blood is lost into the bowel lumen, into the peritoneal cavity, and into the congested wall of the bowel itself, and the patient dies after a few hours just as he would die from a massive internal hemorrhage. The amount of blood lost by the experimental animal in an extensive strangulation has been measured by Holt¹⁹ and by Scott and Wangenstein.²⁷ The strangulated loop is surrounded by a rubber bag (Fig 1), and the amount of blood lost is the sum of the blood in the lumen of the bowel, the blood in the rubber bag around it, and the blood lying in the congested vessels and tissue spaces of the bowel wall itself. The actual amount of blood lost into the lumen and the rubber bag is estimated by the measurement of the hemoglobin content of the fluid in these two situations. The blood lost into the intestinal wall is measured by the increase in weight of the strangulated loop at the time of death. Scott and Wangenstein decided from their experiments that 66 per cent of the total blood volume could be lost in this way. Holt,¹⁹ using a similar technique, estimated the blood loss at 50 per cent in certain cases, and my experiments support these statistics. The estimations of blood loss obtained in my rubber bag experiments⁶ are shown in Table VI.

It has been argued that the rubber bag technique, which was first introduced by Foster and Hausler,¹⁷ gives a false estimate of the amount of blood lost in this condition, since, in strangulation in man, a proportion of the lost volume is reabsorbed by the peritoneum. I have attempted to measure the blood volume directly, however, in animals suffering from massive strangulation,⁷ and have found that the diminution of blood volume after the production of massive strangulation is dramatic (Table VII). When the whole small intestine of an animal is strangulated, there is a reduction of approximately 50 per cent in the blood volume of the animal when death occurs a few hours after the strangulation is induced. The reduction affects the cell volume to a much greater extent than the plasma volume, since, even during the short period of progressive blood loss, an attempt is made to maintain the blood volume by the passage of tissue fluids into the circulation (Chart 7). The effect of massive venous strangulation on blood volume is precisely similar to the effect of a rapid hemorrhage. The clinical application of these experiments is important. The patient suffering from massive strangulation requires blood transfusion, and not the introduction of a mere pint of blood, but the addition from donors

TABLE VI

SHOWING THE AMOUNT OF BLOOD APPARENTLY LOST INTO A STRANGULATED LOOP SURROUNDED BY A RUBBER BALLOON

The loss of one-third of the blood volume by hemorrhage is serious, and loss of one-half of the blood volume by hemorrhage is likely to be fatal (By permission of the Edinburgh Medical Journal)

No of Exper	Fraction of Jejunum-Ileum Strangulated	Weight of Balloon plus Content (Gm)	Weight of Balloon plus Normal Loop of Equal Length (Gm)	Weight of Blood Lost (Gm)	Estimated Blood Volume (Cc)	Blood Loss as Percentage of Whole Blood Volume	Duration of Life
1	One-half	170	60	110	210	52	Died in 24 hrs
2	One-half	220	140	80	188	43	Died in 24 hrs
3	Two-sevenths	132	90	42	120	35	Killed after 18 hrs
4	One-quarter	193	154	39	172	23	Killed after 24 hrs
5	Two-ninths	184	142	42	158	27	Killed after 18 hrs
6	Two-ninths	160	107	53	165	32	Killed after 18 hrs
7	One-fifth	142	111	31	135	23	Killed after 18 hrs
8	One-fifth	203	151	52	188	28	Killed after 24 hrs
9	One-seventh	173	140	33	150	22	Died after 20 hrs

TABLE VII

VENOUS STRANGULATION

EFFECT OF STRANGULATION ON THE BLOOD VOLUME, PLASMA VOLUME AND CELL VOLUME

It will be seen that in the longer strangulations the blood volume may be reduced to approximately one-half of its normal level. The cell volume is proportionately more reduced in most cases than the blood volume, as there is an attempt at replacement of the lost blood by the passage of tissue fluids into the circulation, just as after a rapid hemorrhage. In short strangulations, the plasma loss exceeds the blood loss, these animals live for a relatively long period, and suffer severely from vomiting before death.

No of Exper	Amount of Small Intestine Strangulated	Duration of Life	Mean Blood Volume (Cc)	No of Preoperative Readings	Reduction in Blood Volume	Reduction in Plasma Volume	Reduction in Cell Volume
1	Whole length	7¼ hrs	870 ± 16%	9	44%	37%	47%
2	Whole length	2½ hrs	430 ± 8%	9	52%	50%	59%
3	One-third	12 hrs	740 ± 9%	7	30%	16%	50%
4	One third	5 hrs	1,170 ± 10%	5	49%	30%	66%
5	One fifth	5 hrs	1,240 ± 4%	10	40%	30%	55%
6	One-third	5½ hrs	1,480 ± 7%	7	43%	27%	68%
7	One-tenth (approx)	24 hrs	1,060 ± 9%	5	17%	30%	8%
8	One-twentieth (approx)	4 days	2,150 ± 2%	5	15%	21%	10%
9	One-fortieth (approx)	12 days	1,570 ± 11%	8	Nil	Nil	Nil

INTESTINAL OBSTRUCTION

of an amount of blood equivalent to almost one-half of the patient's blood volume. Massive strangulation, extensive mesenteric thrombosis, for example,

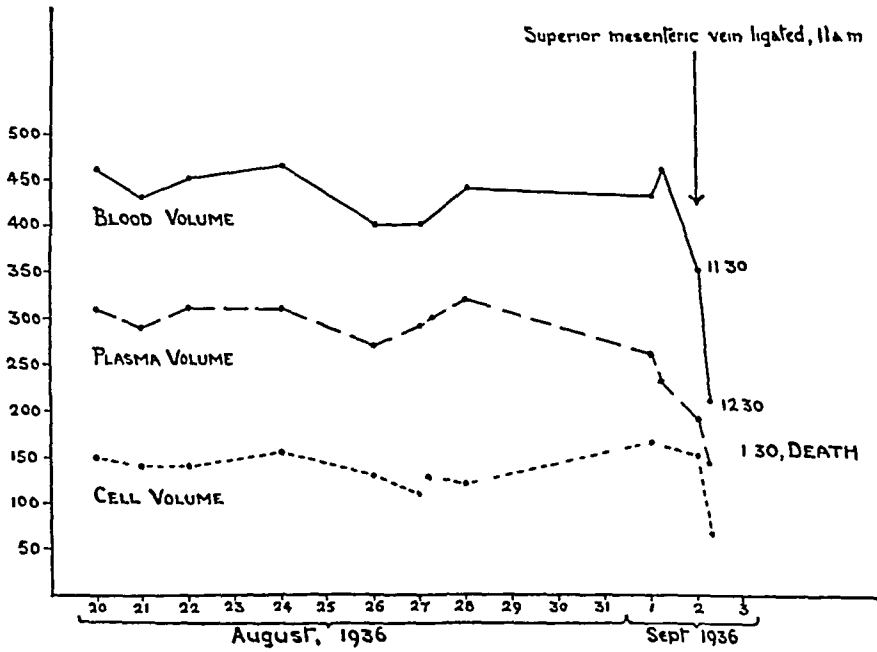


CHART 7—Dog Weight 6.8 Kg. Massive venous strangulation. Death in two and one half hours. Blood volume reduced by 52 per cent, cell volume by 59 per cent, at time of death. (By permission of the British Journal of Surgery.)

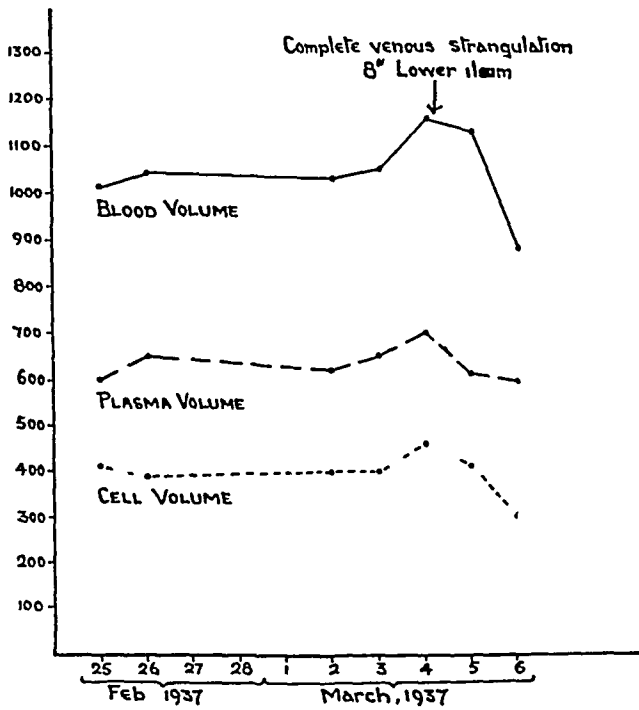


CHART 8—Dog Weight 17.5 Kg. Medium loop strangulation. Slight terminal reduction in blood volume insufficient to be responsible for death. (By permission of the British Journal of Surgery.)

requires massive transfusion, and operation is justifiable only after the blood volume has been restored to an approximately normal level.

(3) *Strangulation of Loops of Medium Length*—Blood loss from the general circulation, while sometimes considerable in this form of strangulation, is not sufficiently great to account for death. The effect on the blood volume is not, as a rule, remarkable. In an animal suffering from strangulation of one-fortieth of its small intestine, there was no alteration in the blood volume, in the plasma volume, or the cell volume, at the time of death. In an animal with one-twentieth of the small intestine strangulated, there was a 15 per cent reduction in blood volume, in an animal with one-tenth of its small intestine strangulated a reduction of 17 per cent in the blood volume at the time of death (Chart 8), and the cell reduction in these cases was inconsiderable, the great part of the depletion of blood volume being due to a loss of plasma (Table VII).

Foster and Hausler¹⁷ first showed that the cause of death in medium loop strangulation is the absorption by the peritoneum of toxic material which has its origin in the strangulated loop. If a loop of small intestine of medium length is isolated, and intestinal continuity reestablished by anastomosis, and if the isolated loop is now surrounded by a rubber bag and strangulated by a ligature tied around the neck of the bag where it encircles the mesentery of the isolated loop, the experimental animal may survive indefinitely (Fig. 1). Foster and Hausler showed, further, that the blood stained transudate which collects in the rubber bag, and which, in the absence of the bag, would be absorbed by the peritoneum, has a toxic effect when injected into other animals. Holt¹⁹ also made an extensive study of the toxicity of the peritoneal transudate from strangulated loops of medium length, and came to the conclusion that two separate toxic elements were present—one which passed outwards from the loop almost immediately after the establishment of strangulation, and which he considered a product of abnormal tissue metabolism, the other a late addition to the transudate, and apparently bacterial in origin. If a chemical fractionation is performed of the transudate collected in one of Foster and Hausler's rubber bags, it is found that two of the chemical constituents of the transudate appear to exercise a toxic effect. One of these is contained in the diffusible fraction of the transudate, while the other is precipitated with the euglobulins. The transudate exercises a considerable depressor effect on the blood pressure when injected intravenously in any anesthetized animal, and attempts have been made to identify the depressor substance concerned.^{3, 9, 19, 23, 33} Early measurements of the histamine content of the transudate by biologic assay suggested that a high proportion of histamine was present in the transudate from strangulated loops, and the total histamine content of the transudate from an eight-inch strangulated loop in a cat was considered then to amount to as much as 4 mg. in some cases. High as this concentration appeared to be, it did not entitle histamine to be regarded as the sole lethal factor, or, indeed, as an important lethal factor, in intestinal strangulation, for the gradual absorption by the peritoneal cavity of 4 mg. over a period of 24 hours would exercise no effect on the animal concerned. Maycock,²³ with a more recent technic of histamine assay, estimated the histamine content of the fluid collected from nonviable strangulated loops to be from 0.3

to 20 gamma per cc, with a maximum total of one-sixth of a milligram in the whole amount of fluid collected, he further estimated the choline percentage at from 8 to 75 gamma per cc of fluid. Maycock concluded that these amounts of histamine and of choline were sufficient to explain the depressor effect of the peritoneal fluid collected from strangulated intestine, but were not sufficient to account for death in that condition. He tended to minimize the importance of a toxic element in the peritoneal transudate. He found that the slow intravenous infusion of peritoneal transudate into normal anesthetized animals has usually no depressor effect upon the blood pressure, although in six out of ten of Maycock's experiments the animal into which the transudate was poured died. Maycock was disinclined to believe that the toxicity of the peritoneal transudate, even in association with the serious depletion of blood volume which sometimes occurs in these animals, was responsible for death in intestinal strangulation. His grounds for this view were that in ten cats, in whom strangulation transudate was injected intraperitoneally after removal of from 51 to 73 cc of blood, only three cats died, and the remaining cats appeared to be unaffected. It seems clear from Maycock's experiments that the histamine and choline content of peritoneal fluid is not of sufficient amount to be an important lethal factor in strangulation, yet the toxicity of this fluid is well established, and appears to lie, as I have said, partly in the diffusible fraction, partly in the euglobulin fraction of the transudate.

The toxicity of the transudate appears to depend upon the presence of bacteria within the strangulated loops. Closed loops of dead sterile bowel taken from newborn guinea-pigs, a few hours after birth, and transplanted into the peritoneal cavities of other animals, disappear without trace and without injury to the host (Table VIII). Dead, closed loops from older guinea-pigs, similarly transplanted, contain both aerobic and anaerobic organisms, and lead to the death of their hosts within a few hours, without peritonitis. The recipient animals die in these circumstances because of the nonviability of the transplanted loop, in combination with the bacteria which it contains.⁴

TABLE VIII

EFFECT OF TRANSPLANTATION OF BOWEL FROM NEWBORN GUINEA-PIG INTO CAT

In Expts 1, 2 and 3, the transplanted small intestine is sterile, and disappears in the peritoneal cavity of the host without trace and without effect. In Expts 4 and 5, the host died—without peritonitis, but apparently from the absorption of toxins from the dead transplanted and infected loop of older guinea-pigs

No of Expt	Age of Guinea-Pig Donor	Culture of Content of Guinea-Pig Bowel	Effect of Transplant on Cat Host	
1	8 hrs	Sterile	No ill effects	Indefinite survival
2	32 hrs	Sterile	No ill effects	Indefinite survival
3	56 hrs	Sterile	No ill effects	Indefinite survival
4	72 hrs	Aerobes and anaerobes	Died 24 hrs	Transplanted bowel distended No peritonitis
5	96 hrs	Aerobes and anaerobes	Died 20 hrs	Transplanted bowel distended No peritonitis

TABLE IX

RELATION OF BACTERIA TO THE TOXICITY OF THE PERITONEAL TRANSUDATE IN STRANGULATION

Development of toxicity in peritoneal transudate from strangulated loops Transudate from early strangulations is nontoxic, and the seromuscular coat from the strangulated bowel in these is sterile Transudate from later strangulated loops is toxic, and the outer coats of the strangulated bowel, though not necessarily the transudate itself, are infected

Length of Bowel Strangulated	Length of Survival Period	Results of Intraperitoneal Injection of Balloon Fluid	Cultures of Seromuscular Coat	Cultures of Balloon Fluid
Whole small intestine	Died in 6 hrs	Whole amount nontoxic to guinea-pig	Sterile	Sterile
1 foot ileum	Killed in 8 hrs	"	Sterile	Sterile
1 foot jejunum	Killed in 10 hrs	"	Sterile	Sterile
1 foot ileum	Killed in 12 hrs	"	Sterile	Sterile
1 foot jejunum	Killed in 15 hrs	"	Sterile	Sterile
1 foot ileum	Killed in 18 hrs	"	Sterile	Sterile
1 foot jejunum	Killed in 18 hrs	"	Sterile	Sterile
1 foot ileum	Killed in 18 hrs	"	Sterile	Sterile
2 1/2 feet jejuno-ileum	Died in 24 hrs	"	Sterile	Sterile
1 foot jejunum	Killed in 30 hrs	Whole amount killed cat in 8 hrs ^{1 2 3 5}	Aerobes and anaerobes	Aerobes and anaerobes
1 foot ileum	Killed in 18 hrs	5 cc killed g-p in 8 hrs ^{1 2 3 4} 2 cc killed mouse in 2 hrs	Aerobes and anaerobes	Sterile
2 1/2 feet jejuno-ileum	Died in 24 hrs	2 cc killed g-p in 4 hrs ¹	Aerobes and anaerobes	Aerobes and anaerobes
1 foot ileum	Killed in 24 hrs	5 cc killed g-p in 7 hrs ^{1 2 3}	Aerobes and anaerobes	Aerobes and anaerobes
9 inches ileum	Died in 20 hrs	5 cc killed g-p in 6 hrs ^{1 2 5} 2 cc killed mouse in 2 hrs	Aerobes and anaerobes	Aerobes and anaerobes
1 foot ileum	Killed in 24 hrs	5 cc killed g-p in 8 hrs ^{1 2 3 4}	Aerobes and anaerobes	Aerobes and anaerobes
1 foot ileum	Killed in 20 hrs	5 cc killed g-p in 6 hrs ^{1 2}	Aerobes and anaerobes	Sterile
1 foot ileum	Killed in 27 hrs	4 cc killed g-p in 5 hrs ^{1 3 4 6}	Aerobes and anaerobes	Aerobes and anaerobes

Symptoms in Injected Animals

- ¹ Apathy, weakness, increased respiratory rate before death At autopsy no peritonitis
- ² Autopsy showed marked congestion of liver and spleen
- ³ Spastic seizure of hind limbs before death
- ⁴ Intense respiratory embarrassment before death Autopsy showed emphysema
- ⁵ Velvety red congestion of duodenum and upper jejunum
- ⁶ Autopsy showed subendocardial hemorrhages

The importance of bacteria in strangulation is further demonstrated by the fact that in the earlier stages of strangulation, when the peritoneal transudate has not yet become toxic, the outer layers of the wall of the strangulated bowel are sterile, as is, also, the peritoneal transudate itself This can be easily

shown by the strangulation of bowel loops in rubber bags, if, at the time the fluid is collected, a biopsy specimen be obtained, with sterile precautions, from the seromuscular coat of the bowel, without opening the lumen (Table IX) If the fluid has become toxic, the seromuscular coat of the bowel gives a growth of aerobes and anaerobes in every case. In most, but not in all, of these later strangulations, the peritoneal transudate itself also gives a growth of organisms. The conclusion is inescapable that death in medium loop strangulation is due to infection of the devitalized bowel by bacteria from its lumen, and to the absorption by the peritoneum of the toxic products of their growth. It seems likely that the toxic euglobulin fraction of the peritoneal transudate contains the actual toxins of the bacteria, while the toxic diffusible fraction of the transudate contains the by-products of tissue destruction.

Knight²¹ has shown that depressor substances are present in human cases of strangulation, not only in the peritoneal fluid, but in the blood within the veins of the strangulated segment of intestine. Knight and Slome²⁰ have further demonstrated that, in cases of strangulation, while the affected bowel loop still remains viable, a toxic effect is demonstrable in fluid obtained from the thoracic duct. In clinical cases of strangulation in man, it seems likely that death is due to a complex combination of pathologic factors, which include (1) Diminution of effective circulating blood volume, in some cases at least, by loss of blood into the lumen of the strangulated bowel, into the bowel wall, and into the peritoneal cavity, (2) absorption of toxic transudate by the peritoneal cavity, (3) absorption of toxic material from the tissue spaces of the affected segment of bowel by lymphatic paths until these become closed as a result of circulatory stasis. It is common knowledge that a strangulated external hernia is a much less serious condition than strangulation of a bowel loop within the peritoneal cavity. This is almost sufficient clinical proof of the importance of peritoneal absorption of the toxic transudate. The sac of a hernia is capable of only slight absorption of the transudate from the strangulated loop which it contains.

Mention has been made in an earlier part of this paper of the depressor effect which sometimes follows relief of a simple occlusion of the bowel. An even more marked depressor effect occurs, in many cases, after relief of a still viable strangulation. Knight found, in animal experiments, that release of viable strangulations produced circulatory collapse and death in not less than 15 per cent of the animals used.²¹ Here again, it would appear that during early strangulation, and the venous congestion which it produces, toxic materials from the lumen succeed in diffusing into the tissue fluids of the wall of the strangulated bowel, but fail to enter the general circulation, because of venous obstruction. When, however, the strangulation is relieved, the veins of the affected segment of bowel empty, circulation returns, and the toxin-laden fluid within the wall of the strangulated bowel can now reach the general circulation, to exercise a toxic, and sometimes lethal effect. In fatal cases of strangulation in man, operation has nearly always been performed. At operation, the strangulated loops of bowel are closely inspected for signs of non-

viability If the bowel appears to be viable, even though still congested, it is returned to the abdomen, and gradually, thereafter, recovers its normal circulation It has long been known that whenever there is any doubt about the viability of a strangulated loop, it can be returned to the abdomen, as a rule, without any risk of gangrene and peritonitis I would submit that the main risk in returning a strangulated loop to the abdomen is not the risk of perforation of that loop, but the danger that, in recovering its viability, there may be a return of toxic material from the wall of the strangulated bowel This is a strong argument in favor of the more frequent resection, or, at least, exteriorization, of strangulated intestinal loops "All recent experimental work has gone to show that when the least doubt exists as to the viability of the bowel, resection should be practiced, as continued toxemia from autolysis of cells and potential obstruction from imperfect peristalsis may lead to death some days after operation" (Wilkie³⁶)

CONCLUSIONS

In high small intestine occlusion, the cause of death is dehydration, hypochloremia, alkalemia, and azotemia These can be effectively controlled by nasal suction drainage and forced intravenous saline by drip Operation may be delayed, and conservative measures continued for many days before operative relief of the obstruction, provided the cause of obstruction is known, and provided the presence of a strangulating element can be definitely excluded

In untreated cases of low small intestine occlusion, whether in the experimental animal or in man, death does not occur, as a rule, until three or even four weeks after the onset of obstruction In these cases, suspended absorption of water, salts, food materials, and other constituents of the intestinal content is sufficient to explain death Gross congestion of the bowel is sometimes considerable before death in these cases, and leads in some, but not in all, animals to depletion of the blood volume Perforation of the distended bowel and peritonitis is a relatively frequent cause of death in the animal or man whose occlusion remains unrelieved by operation

To-day, the deaths from low small intestine occlusion are nearly all post-operative deaths The toxic effect of sudden relief of a long-continued distention of the bowel has been demonstrated by experiment

In occlusion of the colon, perforation and peritonitis are responsible for death in most cases In long-continued colonic occlusion, the same factors probably operate as operate in low small intestine obstruction

In closed loop obstruction, the cause of death depends upon the infectivity of the contents of the loop In the case of the heavily infected closed loop, death is due to perforation and peritonitis In the mildly infected closed loop, the same morbid influences are present as in low small intestine occlusion Splanchnic congestion is usually more serious in closed loop than in simple occlusion

In strangulation of short loops of bowel, death is due to perforation and peritonitis

In long loop strangulation, death is due to diminution of the effective circulating blood volume, as a result of blood loss into the lumen and wall of the strangulated intestine, and into the peritoneal cavity

In strangulation of loops of medium length, the cause of death appears to be the absorption of toxins. In the early stages of strangulation, this is by way of lymphatic routes, later by way of the peritoneal cavity

The depressor effect of the sudden relief of any form of intestinal distention is seen in an exaggerated form upon the sudden relief of a long-continued strangulation

A method is described of the establishment of chylothorax in the experimental animal, to furnish reservoirs of chyle for the purpose of experimental chyle transfusion

The later experiments recorded in this paper have been performed in the Department of Surgery of the University of Edinburgh, under the direction of the late Sir David Wilkie, and of the Deputy Director, Mr W C Wilson, now Regius Professor of Surgery in the University of Aberdeen. Many of the earlier experiments were performed in the Department of Surgery of Washington University, St Louis, under the direction of Dr Evarts A Graham, and with the guidance of Dr Robert Elman. The American experiments were performed during the tenure of a Rockefeller Traveling Scholarship, and the later part of the work in Scotland has been subsidized by a grant from the British Medical Research Council

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THE MUSCULAR ACTIVITY OF THE SMALL INTESTINE, IN THE DOG, DURING ACUTE OBSTRUCTION

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STONE AND FIROR, in 1924, reported that in cases of temporary obstruction of the terminal ileum in the human (duration five hours or less), pressure within the ileum rose as high as 150 cm of water, and suggested that the extremely high pressure in obstructed intestine contributes to the toxemia, probably by facilitating absorption of hypothetical toxins. Heirin and Meek² have further emphasized the importance of pressure in the pathologic mechanism by producing symptoms of obstruction in dogs by the inflation of balloons within the intestine to pressures of approximately 100 Mm Hg (135 cm aq). It has been shown, however, that if by-passes are provided so that balloons inflated to these pressures do not actually obstruct the intestine, the animals go on to death without a significant lowering of blood chlorides³. Since hypochloremia is one of the cardinal signs in obstruction in dogs, and since life may be greatly prolonged by administering chlorides,² it may be doubted that the pathologic mechanism in dogs dying from overdistention of intestinal balloons is identical with the mechanism in dogs dying from other forms of obstruction.

The clinical significance of much of the experimental work which has been done in the dog with overinflated balloons remains obscure unless it can be established that pressures of similar magnitude develop within the intestine obstructed by ligation or simple occlusion of the lumen. There is no question that closed loops and the entire bowel above a simple occlusion become distended with gas and secretions in the dog as well as in the human. That strangulation may result from overdistention was first suggested by Van Zwahlenburg,⁴ in 1907. Data obtained in this laboratory show, however, that distending pressures must usually rise above 30 Mm Hg in dogs under barbital anesthesia before there is reduction in blood flow⁵. In the light of these data, it would appear that distention may produce damage by ischemia only if it rises, during the course of obstruction, above a certain critical level. Since the circulation through active and inactive intestine may not be equally affected by a given distending pressure, the question of adynamic ileus as a constant terminal phenomenon in obstruction has more than academic interest.

The pressures which have been reported to occur within obstructed small intestine in the dog are considerably below those used in experiments with overinflated balloons. Owings, McIntosh, Stone, and Weinberg⁶ found

average 'tone, or resting pressure in simple obstruction to be 6–8 cm aq, with pressure rising to 30–60 cm during maximum contractions. In closed loops Burget, Martzloff, Suckow, and Thoin-ton⁷ measured an average pressure of 39.5 cm aq. Sperling, Paine, and Wangenstein⁸ found pressures from 4 to 19 cm aq in simple obstruction of the lower ileum.

Hypermotility during the early stages, and adynamic ileus, as a terminal phenomenon, have come to be clinically accepted as characteristics of the obstructed bowel. In experimental obstruction, hypermotility has been observed more frequently than ileus,^{6 8 9} and in studies in which attention has been directed to this detail, terminal ileus appears to be associated with peritonitis.⁶ There is, thus, no evidence for terminal ileus in uncomplicated obstruction in the dog.

In view of the importance of these details for an understanding of the immediate pathologic mechanism in obstruction, and the incomplete information available, we thought it worth while to make a more extended study of muscular activity in obstructed intestine in the dog.

Methods—All operations were performed on healthy adult dogs under ether anesthesia, with strict asepsis. At the time of operation a large condom balloon was inserted through a stab-wound in the antimesenteric border of the intestine so as to lie in an obstructed segment. This was accomplished by passing the balloon in an oral direction and tying the obstructing ligature (soft, round cotton yarn) tightly down upon its lead tube, the latter being made rigid by insertion of a short length of glass tubing. The stab-wound, about 1 cm below the obstructing ligature, was then closed about the lead tube by Witzel's method. This procedure avoided the placement of a suture line, through which leakage might occur, in obstructed intestine.

In some animals a balloon was also placed, at the same time, in distal unobstructed intestine through a stab-wound about 5 cm below the first, the balloon being passed in an aboral direction. The lead tubes from the balloons were brought out and anchored in the belly wound which was closed in the usual manner.

Most of our observations were made upon dogs with closed loops of the first portion of the jejunum, about 15 cm below the ligament of Treitz, prepared by simple ligation at this level, with a second ligation upon the lead-tube of the recording balloon 10–12 cm below, the balloon lying between the two ligatures. It was intended to compare these closed loops with simple obstructions, in which it is generally agreed that pressure is lower. But our data on the closed loops showed such low pressures that we felt a complete comparison unnecessary.

That necrosis and perforation at the ligature will occur with this type of obstruction, if the animal survives long enough, is generally agreed. Most of our animals died 48–72 hours after operation, the short survival time being, doubtless, in part due to the fact that we gave no fluids or other supportive treatment. Autopsies were performed as soon as possible after death in all. Ten animals out of a series of 27 were found to have perforated

loops In the others there was no demonstrable perforation or peritonitis With these exceptions, therefore, our data may be taken as showing the course of events leading to death from uncomplicated obstruction

All observations were made without anesthesia, with the animal, after a brief period of training, lying quietly on a pad The first observation was made 4-24 hours after the operation, and subsequent observations were made at intervals of 8-18 hours Preliminary to making an observation, the balloons were inflated and deflated a few times to make sure that they were not twisted or kinked, completely emptied of air under negative pressure, then filled from a syringe with 15 cc of air measured at atmospheric pressure The lead tubes were then connected with water manometers, and a kymograph record, lasting 75-120 minutes, was made Since the balloons had a tested capacity of 50 cc at atmospheric pressure outside the intestine, their pressure readings at a volume of 15 cc are approximately equal to intra-intestinal pressure Complete expulsion of the 15 cc of air from the balloon into the manometer gave a pressure reading in the manometer of approximately 40 cm aq, which is higher than our highest measurements

Any attempt to express a change in intestinal motility in quantitative terms, is open to the criticism that the features chosen for quantitation may not be representative All workers in the field have observed simultaneous changes of different degree or direction in such various indices of motility as tone, contraction height, size and frequency of tonus waves, and rhythmicity of pendular movements In the absence of any general agreement upon some one satisfactory index to intestinal motility, we have made separate measurements of these individual functions as defined below

Results—Minimum Pressure This was measured as the lowest pressure recorded at any time during each period of observation Since it is read during the interval between contractions, it represents what would usually be called minimal "tone" for each tracing

In ten animals who were prepared with balloons in the distal, unobstructed jejunum for comparison, we were able to make a total of 25 comparative readings of minimum pressure in obstructed and unobstructed intestine In 19 of these paired observations, minimum pressure was significantly higher in the obstructed loop In every animal except one, minimum pressure was elevated in the obstructed loop over its unobstructed control on the first reading (Table I)

As will be seen from examination of Table I, our irregular intervals of observation fail to show the time required for pressure to reach its peak in the obstructed loops Nineteen animals appear in the table upon whom more than one observation was made In eight of these, pressure was highest at the first reading It is possible that the peak of pressure has escaped observation in some, but this is unlikely since, with a few exceptions, there is close agreement of the readings at the peak of the pressure elevation

The average of the minimum pressures at the time of their greatest elevation (series of 27 dogs) was 16 cm aq The highest observed minimum

pressure was 27 cm aq. As was expected, the average of the closed loops was somewhat higher than the average of the small series of simple obstructions (four animals—average minimum pressure at peak of elevation 14.5 cm aq.) The average of the minimum pressures at the time of their greatest elevation in the ten dogs with balloons in distal, unobstructed jejunum was 10.0 cm aq.

TABLE I

Dog No	Segment	Minimum Pressure					Maximum Pressure					Contractility					
		Obs	No	Cm Water				1	2	3	4	5	1	2	3	4	5
				1	2	3	4										
1	Distal		9	8	9	5		10	10	16	7		9	10	8	23	
	Obstr —(p)*		17	14	16	3		32	26	28	25		65	55	11	52	
2	Distal		10					12					4				
	Obstr —(p)		14					19					17				
3	Distal		8	9				9	10				8	14			
	Obstr		9	12				17	30				20	90			
4	Distal		8	8				16	24				26	46			
	Obstr —(p)		14	9				30	12				50	11			
5	Distal		9	10	11	11		13	12	16	14		7	5	9	11	
	Obstr —(p)		11	27	3	5		15	28	11	7		10	5	5	4	
6	Distal		6	5	—	—		8	6	—	—		8	4	—	—	
	Obstr		10	18	14	15		13	23	17	28		9	20	8	55	
7	Distal		6	19	—			13	23	—			12	15	—		
	Obstr		18	14	6			26	20	14			18	20	42		
8	Distal		11					12					2				
	Obstr		24					26					3				
9	Distal		8	9	12			9	10	17			5	5	11		
	Obstr —(p)		8	—	11			14	—	16			30	—	7		
10	Distal		13	8	12	5	12	17	11	14	6	14	13	5	3	3	3
	Obstr		23	11	12	12	15	26	15	17	22	26	17	15	17	40	50
11	Obstr		12					14					8				
12	"		20	7				22	8				11	7			
13	"		9	10	9	10		11	12	22	33		10	17	46	80	
14	" —(p)		14	12	10			19	23	17			15	31	35		
15	" —(p)		12	5				15	12				3	27			
16	"		3	12	8	13		6	31	30	31		11	65	75	56	
17	"		6					9					17				
18	" —(p)		18	10				24	11				31	2			
19	"		19					20					10				
20	"		6	8				28	27				65	48			
21	"		5	9				9	24				16	28			
22	"		7					21					35				
23	"		4	13	15	8	7	6	28	25	15	15	4	55	40	34	38
24	"		18	17	16			30	28	21			5	3	20		
25	" —(p)		16					19					15				
26	" —(p)		21					27					28				
27	"		15	25				23	28				15	8			

* p denotes perforation demonstrated at autopsy

Of the 19 animals, upon whom serial observations were made, nine showed a definite diminution in minimum pressure toward the end of their survival period. In six of these, perforation was found at autopsy. Neither perforation nor peritonitis could be demonstrated at autopsy in any of our other animals.

Maximum Pressure—This was taken as the highest pressure recorded at any time during each period of observation. Respiratory records were taken routinely by means of a pneumograph to ensure that our readings of maximum pressure were not influenced by such modified respiratory acts as vomiting and defecation. The data which we obtained may be taken to

represent the maximum pressure developed within the intestine by the muscular activity of the intestine

In the ten animals with balloons in both obstructed (closed loops) and unobstructed (distal) jejunum, we made a total of 25 paired observations on maximum pressure. In 20 of these, pressure rose higher in the obstructed than in the unobstructed intestine. In all animals, maximum pressure was elevated in the closed loop over its distal control at the first observation (Table I). In the entire series of 27 dogs, the average of the maximum pressures taken at the time of their greatest elevation was 26.8 cm aq, the highest single reading being 33.0 cm. Of the 19 dogs available for serial observations, only nine showed a terminal fall in maximum pressure. As shown in Table I, these are, with two exceptions (Dogs 7 and 24), the animals whose minimum pressure declined terminally, and in whom perforation was demonstrated at autopsy. That perforation does not necessarily suppress contractility is shown by the observations on Dog 15, in whom perforation was demonstrated at autopsy two and one-half hours after the last observation was made. Only three of the animals with terminal decline in contractility were prepared for observations on distal intestine (Dogs 4, 5 and 9). In none of these was contractility suppressed terminally in the distal control intestine (Table I).

Contractility—It is obvious that intra-intestinal pressure may be either a function of the muscular activity of the intestine, or the result of passive stretching of the walls of the intestine by its contents. Pressure is, therefore, an uncertain index to the muscular activity of the intestine. Nor are the pressure changes (obtained by subtracting minimum from maximum pressure) much more reliable, since under some conditions intense muscular activity may result in the maintenance of steady high pressure for long periods of time, and since, on the other hand, secretion, transudation, or hemorrhage may cause rather abrupt changes in the volume of intestinal contents. Clearly recognizable muscular functions of the jejunum result in the appearance on the pressure records of (a) simple pressure waves at a frequency of 6–20 per minute, due to the pendular movements, and (b) tonus waves with a duration of 1–3 minutes, upon which the pressure record of the pendular movements is superimposed. We have measured the amplitude in each tracing of these two types of pressure change, and have taken as a measure of contractility the maximum pressure change of either type, which occurred during each period of observation. These pressure changes are recorded in Table I under “contractility” without distinction between the two types.

Twenty-six paired observations on obstructed and unobstructed intestine were made in ten dogs. Maximum contractility as measured in this manner was greater in the obstructed than in the unobstructed intestine in 22 observations. Among the 19 dogs upon whom serial observations were made, there was a definite terminal reduction in contractility in only six animals (Dogs 4, 5, 9, 12, 18 and 27). Four of these (Dogs 4, 5, 9 and 18) showed

a terminal fall in minimum pressure, and were found at autopsy to have perforated loops

Rhythmicity—The rhythm recorded by the pendular movements on large balloons, such as we used, is of doubtful significance. A rapid beat on the record may mean a rapid beat of a single fascicle of smooth muscle, or it may mean the summation on the record of a number of slowly beating fascicles contracting and relaxing asynchronously. The use of smaller balloons, or of enteriographs recording smaller areas of smooth muscle, reduces, but does not remove this error. We obtained data on rhythmicity as recorded by the pendular movements on our records, fully aware that our methods were inadequate, in the hope that some striking change might be observed which would justify an attempt at interpretation. Since this hope was not realized, the possibility remains that adequate studies on rhythm would show striking changes in obstruction.

In our studies, the rhythm of the pendular movements appeared to be at a maximum during the intervals between tonus waves. The average for all dogs, in the unobstructed distal jejunum, at this time was 16.2 beats per minute, in the obstructed, closed loops, 16.3 beats per minute. Usually there was appreciable slowing of rhythm on the records toward the peaks of tonus waves. The average for all dogs at this time in the unobstructed distal jejunum was 14.2 beats per minute, in the obstructed loops 12.7 beats per minute. Examination of individual pairs of observations fails to show a consistent difference in the rhythm of the obstructed and of the unobstructed intestine. Out of 24 such paired observations on minimum rhythm (at the peaks of the tonus waves) the rhythm was greater in the obstructed loop, eight times, greater in the unobstructed loop, ten times, and the same in both, six times. Out of 22 observations on maximum rhythm (at the troughs of the tonus waves) rhythm was greater in the obstructed loop 16 times, in the unobstructed loop, five times, and the same in both, once.

Effect of Epinephrine on the Obstructed Intestine—Data on the response to intravenous epinephrine were obtained in an attempt to determine (1) Whether the increase in minimum pressure in the obstructed intestine is due entirely to distention of the intestine by an increase in its contents, and (2) whether the increase in contractility is due to diminished sensitivity to inhibitory agents.

To answer the first question, we injected moderately large doses of epinephrine (usually 0.02–0.04 mg. in a volume of 1 cc.) at a time when minimum pressure was markedly elevated. In a series of 24 animals, studied in this way, epinephrine caused a significant drop in minimum pressure in the obstructed loop in every case (Graph 1).

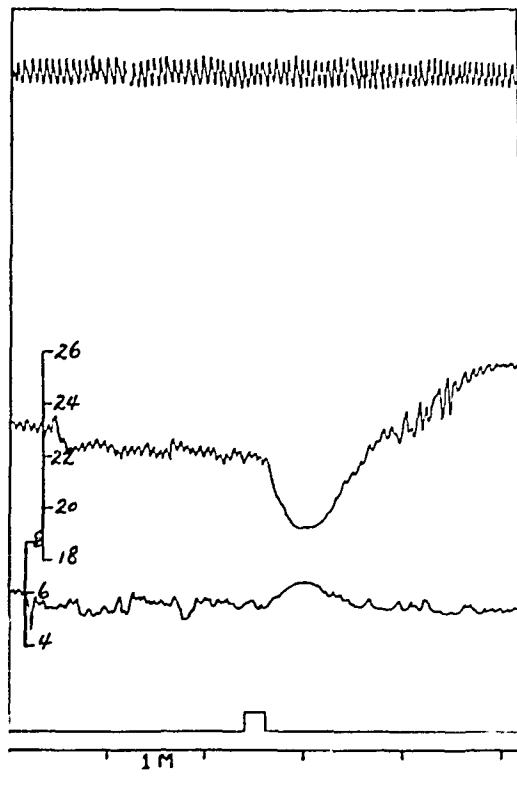
To answer the second question, we determined the threshold dosage of epinephrine, under standard conditions, in a series of six dogs at intervals during the survival period. All of these animals were prepared with balloons in distal, unobstructed intestine for comparison. All doses were made up in a volume of 1 cc. and injected as rapidly as possible in the posterior crural

vein The doses were adjusted at each observation until a just-detectable reduction in either tone or contractions was obtained, and each dose near the threshold was repeated two or more times to check the determination. No consistent difference in the threshold for the obstructed and the unobstructed intestine at any time during the survival could be established in this series of animals. In all six animals, however, there appeared to be a progressive lowering of the threshold in both the obstructed and the unobstructed intestine (Table II).

Discussion—It was not our purpose in this study, to maintain animals surviving obstruction in optimum clinical condition. It is possible that our results would have been somewhat different had we done so. Our data show, however, that dogs may go on to death without the development, even in closed loops, of excessively high intra-intestinal pressures. Such pressures as we have observed do not, in anesthetized dogs, reduce the total blood flow through the intestine.⁵ They are far below the pressures employed in obstructing balloons for the production of symptoms. Whether these moderate pressures, maintained in non-obstructing balloons, will produce symptoms in the dog has not yet been determined.

That our data on the pressures prevailing in obstructed intestine are fairly accurate is shown by their approximate agreement with the statistics of previous workers.^{7, 8, 9} It might be expected that our readings would be high, since our methods required the inflation of a balloon within the loop, thus increasing the volume of intestinal contents. That they are somewhat lower than those previously reported⁷ for closed loops may be due to the absence of supportive postoperative treatment in our dogs. Details of postoperative treatment are not given in most of the previous reports.

Our data suggest, in confirmation of Owings, McIntosh, Stone, and Weinberg,⁶ that terminal ileus is a concomitant of peritonitis rather than of obstruction. In only three animals, in a series of 20, did we find a terminal reduction in muscular activity (using any single criterion of motility) unaccompanied by peritonitis secondary to perforation. In half our animals no terminal reduction in motility was demonstrable.



Graph 1

GRAPH 1.—The Response of the Obstructed Intestine to Epinephrine. Records from above down—Respiration by pneumograph, balloon record of doubly ligated jejunal loop, balloon record of distal unobstructed jejunum. Intra-intestinal pressure in centimeters of water. Duration of obstruction 23 hours. At the signal 0.005 mg epinephrine in 1 cc saline was injected into the posterior crural vein. The rise in pressure in the unobstructed loop is not unusual in atonic intestine.

It is not possible to say, from our studies, whether rhythm in the obstructed intestine is modified. The limitations imposed by our methods were pointed out above. These limitations are such as to permit us to say only

TABLE II
THRESHOLD INTRAVENOUS DOSAGE OF EPINEPHRINE IN OB-
STRUCTED AND IN DISTAL SEGMENTS

Dog No	Duration of Obstruction Hours	Dose (Mg) in 1 Cc	
		Distal	Obstructed
1	9	0.0100	0.0100
	14	0.0081	0.0081
	23	0.0055	0.0055
2	5	0.0028	0.0028
	23	0.0025	0.0010
	33	—	0.0010
3	10	0.0280	—
	28	0.0028	0.0028
	53	—	0.0028
4	8	0.0400	0.0400
	30	0.0280	0.0280
5	12	Motor	0.0280
	28	0.0020	0.0050
	48	0.0033	0.0033
6	23	0.0200	0.0400
	33	0.0050	0.0200
	48	0.0020	0.0020

that we obtained no evidence in favor of Alvarez's¹⁰ hypothesis that a reversal of the rhythmic gradient is responsible for stasis and vomiting in obstruction, since we demonstrated no such change in the rhythm of the obstructed intestine as his theory requires.

Additional evidence that the adynamia of the obstructed intestine in the terminal stages is far from complete, is adduced from the fact that the intestine may be inhibited by epinephrine. The significance of an apparent increase in sensitivity to epinephrine in both the obstructed and the unobstructed intestine in terminal stages requires elucidation. It seems clear, however, that hypermotility in the obstructed intestine is not due to a loss of irritability to inhibitory agents of this type.

SUMMARY

Balloon studies of motility in obstructed jejunal loops were undertaken in unanesthetized dogs at intervals, so long as the animals survived. Comparisons were made in some animals with motility in unobstructed distal segments. The following data were obtained:

(1) At the time of the greatest increase in intra-intestinal pressure, maximum pressure in the obstructed loops averaged 26.8 cm. aq., with the highest single reading 33.0 cm. aq. Minimum pressure at the time of its greatest elevation averaged 16 cm. aq. The range of pressure in closed loops is con-

siderably above the range in distal, unobstructed intestine (average maximum 156 cm aq, average minimum 100 cm aq)

(2) Contractility was usually considerably greater in the obstructed than in the unobstructed intestine

(3) Neither pressure nor contractility was found to diminish toward the end of the survival period unless perforation occurred. Even in the presence of perforation, active contractions sometimes occurred

(4) No loss in irritability to intravenous epinephrine could be demonstrated in obstructed intestine. Even in terminal stages, the response to sufficiently large doses was a drop in pressure within the intestine, showing persistence of some muscle tone

(5) The bearing of these data on the theory that pressure within obstructed intestine damages the intestine is discussed

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THE SIGNIFICANCE OF NEUROMATOUS LESIONS IN OBLITERATED APPENDICES

A CLINICOPATHOLOGIC STUDY

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THE SURGEON, confronted by the patient with complaints of abdominal pain (epigastric, right lower quadrant or diffuse) temporarily aggravated, encounters symptoms suggestive of appendicitis but is frequently unable to elicit objective evidence of such. Physical examination of these patients may disclose tenderness in the right lower quadrant, most frequently on deep pressure, but rarely muscle rigidity. Temperature levels and leukocyte counts are frequently within normal range. The patient may give a history of long standing abdominal distress, frequently with a recollection of its inception in an episode characterized by acute pain. Often, long standing, mild abdominal discomfort is punctuated by attacks of acute distress, occasionally with some history of slight fever. As frequently, a history of dietary indiscretion is obtained. If encountered in a subjectively quiescent stage or after the subsidence of what historically resembles an acute attack of appendicitis, the patient may, if indicated, be operated upon with a diagnosis of interval appendix, chronic or subacute appendicitis. The pathologic reports are variable, in only some instances consistent with the clinical picture. The clinical entity, chronic appendicitis, only rarely receives strict morphologic confirmation.

On those occasions when the preoperative diagnosis is acute or recurrent appendicitis, the histologic diagnosis is not infrequently at variance with the clinical diagnosis. The attitude of the surgeon may, in such instances, be one of chagrin or confusion. This attitude, however, may be somewhat mollified by his recollection of the operative picture which disclosed to him an explanation of the symptoms which he had interpreted as inflammatory, such as the presence of bands, twists or kinks which may produce mechanical symptoms.

To the confused surgeon and the surgeon-harassed pathologist, the entity "neurogenic appendicitis" should offer a promising solution of these numerous instances of so-called chronic appendicitis. Since its description in 1921, this subject has commanded the attention of a number of authors to whose opposing opinions probably may be attributed the fact that neurogenic appendicitis as an entity has been accepted with some diffidence. Some authors deny its existence and the neurogenous nature of lesions occurring in the involved appendices, others, agreeing to the nervous nature of certain lesions observed

in appendices, question the clinical significance of these or the likelihood of a diagnosis of neurogenic appendicitis being made with certainty preoperatively, the proponents of the entity are clamorous for its further clinical confirmation

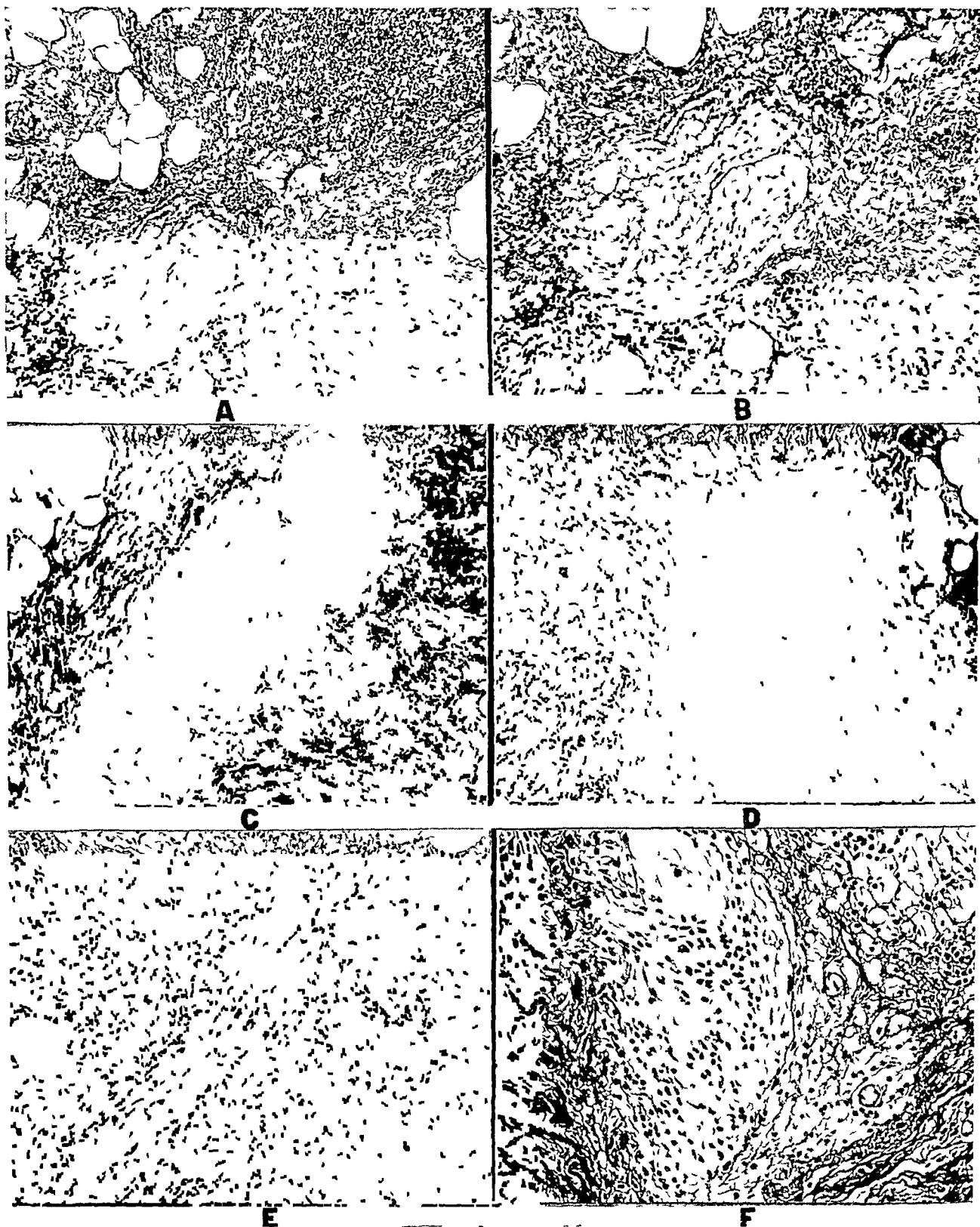
As examples of the varied evaluations of the subject, the following are listed Masson¹ and Maresch,² in 1921, almost simultaneously, described lesions in the obliterated appendix Both authors considered the lesions as sympathetic neuromata Subsequently, Masson³ altered his interpretation of these from sympathetic neuromata, which he had initially likened to amputation neuromata, to argentaffin neuromata The latter he considered to be proliferations of mucosal nervous tissue stimulated by argentaffin cells with which they are associated

Both the above authors regarded these lesions as having been provoked by previous inflammations Masson,³ in 1922, believed that a banal ulcerative process, sufficiently intense to be irritative but sufficiently slight to be non-destructive of the epithelium and contemporaneous with the normal neurogenic impulse, provokes hyperplasia of the preexisting neuro-argentaffin tissue which becomes enmeshed in the cicatricial tissue His original disposition of these structures as amputation neuromata caused by division of the sympathetic filaments of the mucosa by an ulcerative process, he⁴ considered unsatisfactory, in that the neuromata always contain argentaffin cells and amputation neuromata do not contain these Masson⁴ also discussed the possibility of the periglandular plexus from which these neuromata arise being, not of sympathetic origin, but dependent genetically on certain entodermic cells and that it represents a placode, a neuteroderm

Urech,⁵ in 1928, found among 400 appendices removed in the quiescent period after acute attacks of appendicitis, 16 obliterated, in which neural proliferation was prominent Urech stated as a hypothesis that the lesions may be attributed to more or less discrete inflammation which escapes the attention of the patient This author further stressed that the superabundance of nervous tissue which has been wrongly or reasonably compared to amputation neuromata explains the important place that pain plays in this clinical entity and the happy results after operations of patients without inflammatory lesions This author further stated that if the diagnosis could be foreseen preoperatively, it would be affirmed only exceptionally (He also noted that two-thirds of the cases occurred in women, and presented the variety of symptoms which are ordinarily classified as nervous)

Hosoi,^{6 7} in 1933, presented pathologic findings and the clinical features of 344 consecutive cases, 56.7 per cent containing neuromata, 48 per cent of the 344 showing some degree of obliteration These cases were presented as instances of neurogenic appendicitis and were supposedly operated upon because of symptoms which could be attributed to nervous irritation In the histories of many of these patients, previous incidents simulating appendiceal crises were described

Simaid,⁸ in 1935, stated that nervous alterations alone may give rise to



A—Presence of proliferated nerve fibers in the center of an obliterated appendix. Note the accumulation of lymphocytes adjacent to the nerve fibers (Hematoxylin eosin preparation, $\times 60$)

B—Same as A (Hematoxylin eosin preparation, $\times 80$)

C—Large nerve bundles in an obliterated appendix (Masson stain $\times 56$)

D—Presence of nerve bundles adjacent to much lymphadenoid tissue in the center of an obliterated appendix (Masson stain $\times 60$)

E—Lymph follicles and nervous elements in close approximation (Hematoxylin eosin preparation, $\times 80$)

F—Nerve cells and fibers adjacent to old connective tissue fibers in the center of an obliterated appendix ($\times 160$)

characteristic symptoms of acute appendicitis such as stabbing pain, muscle guarding, *etc*. He previously had made the suggestion that in the presence of clinical signs and symptoms pointing to acute appendicitis, when leukocyte count is at or near normal, and disease of the kidney, ovary or gallbladder may be excluded, the diagnosis of neuro-appendicopathy can often be made with assurance.

Fein, Hanan and Seidler,⁹ in 1938, listed 202 neuromata among 600 appendices, 140 occurring in appendices with varying degrees of obliteration. Twelve and one-tenth per cent of neuromata were in appendices showing acute suppurative inflammation, 26.8 per cent were associated with subacute appendicitis.

Llombart,¹⁰ in 1938, in investigating the anamneses of ten patients, stressed that, in general, one might state that definite attacks, often with fever and muscle guarding, precede nervous hypergenesis and that it might be supposed that obliteration was initiated at such a moment and the nerves contained within the obliterated zone hypertrophied. Though this author believed it almost logical to suppose the nervous lesions incitants of the clinical symptoms, he stated that it is impossible at present to know whether repeated attacks (simulating appendicitis) favor the development of neurogenic appendicitis or, on the contrary, the repetitious complaints are the consequence of the nervous lesions. He was impressed with the rapidity with which this nervous hypergenesis was established. This author succeeded in demonstrating nerve fibers by the use of specific silver stains.

Rossle,¹¹ in 1930, pointed out that not only central neuromata in recently obliterated appendices but also neuromatosis of the intact mucosa and submucosa are able to produce appendiceal complaints, the latter largely because of alterations of the neuromuscular apparatus which, in interfering with evacuation, provokes symptoms. However, he considered the neuromata to be proliferations of the Schwann's syncytium and as such but a single feature of pathologic alteration of the nervous apparatus.

Among the opponents of the neurogenous etiology of these structures may be mentioned the following:

Schweizer,¹² in 1922, describing "neuromatige" in obliterated appendices, and presenting pictures of lesions almost identical with or at least very similar to those of Masson,¹ took exception to Masson's interpretation of these lesions. He evaluated them as neurinomata and questioned their relation to symptoms in that many were noted in autopsy specimens from subjects of advanced age. This author further stressed the high incidence of argentaffin cells and was inclined to consider these structures derivatives of the sympathetic fibers surrounding the crypts and the muscularis mucosa.

Schack,¹³ in 1932, believed the so-called neuromata to be, not primary proliferations of nerves, but a disease or alteration of the reticulum, and that the finding of nerve fibers within them is only incidental in that nerve fibers spreading as a net with and between the reticulum cells are only naturally included within a tumor of the reticulum. He considered these irregular

growths the indirect consequence of inflammatory irritation. This author was unable to prove the existence of an anatomic disease in the sense of neurogenic appendicitis and evaluated the neurogenous tissue as a residuum of inflammation.

Collins,¹⁴ in 1936, in reviewing a large number of surgical and autopsy specimens, was unable to find indication of nervous proliferation as the provocative element in obliteration. He considered this largely induced by inflammation which progressed to granulation tissue. Though no illustrations were presented, it was the contention of this author that the axial lesions in obliterated appendices are composed of granulation tissue.

That structures other than adult fibrous connective tissue occur in the axis of the partially or completely obliterated appendix is unquestioned. The interpretation of these may or may not be of merely academic interest. If they are neuromatous in nature the surgeon, cognizant of the confusion involving the mechanism of abdominal pain, asks, "What do they mean, and are they, *per se*, responsible for this pain?"

The presence of nerve fibers in the mucosa of the intestinal tract has been demonstrated by numerous authors, and specifically in the appendix by Reiser,¹⁵ who speaks of a nervous spongiosa. The quantity of these nerve fibers is considered to be so great that some authors think they compose the main mass of the mucosa (Masson¹⁶). However, the possession by these nerves of sensory functions is open to dispute. Thus Hill,¹⁷ from a study of the intestines of animals, concluded that the mucosa and subserosa are endowed with sensory function. Masson¹⁸ likewise attributed to the mucosal fibers sensory functions. He considered "a nervous system peculiar to the intestinal mucosa, of entodermic origin, the neurites of which mingle with those of the sympathetic and form the plexus of the mucosa." This plexus, according to Masson, "contains two kinds of fibers, the one centripetal, belonging to the neurentoderm, the other centrifugal, starting from the sympathetic ganglia and arriving at the intestinal surface." He also stated that, because of the organogenic analogies of the hypothetic system with the argentaffin cells, and the placodic neuro-epithelium of the olfactory mucosa, he had thought that its function might be sensory rather than motor. Histologic studies by many investigators have failed to produce definite evidence of sensitivity, most authors considering this property of the mucosa a possibility rather than a fact. Reiser,¹⁵ Schack,¹³ Oshima¹⁹ and Ranson,²⁰ on the other hand, stated that in spite of the negative character of the histologic evidence, the existence of sensory fibers in the gastro-intestinal mucosa has been assumed by most physiologists. The clinicophysiology evidence would implicate the muscularis rather than the mucosa of the hollow viscera in the sensation of fulness or pain (Hertz,²¹ Ryle,²² Morley,²³ Kuntz,²⁴ *etc*).

It may be of interest in this connection to consider, in short, the present concept of the origin of "appendiceal" pain. Actually most clinicians consider the pain in diseases of the alimentary canal to be most frequently true visceral pain (Capps,²⁵ Hertz²¹). But visceral pain is usually attributed to

muscle tension Most authors consider the only adequate stimulus for this type of pain to be abnormal increase in the tension of the muscular elements produced by distention of the viscus, some suggesting undue contraction which in bringing pressure to bear upon the nerves in the wall of the hollow viscera, may produce pain The pain involved in undue contraction, however, is generally considered to be the result of distention of a neighboring segment of bowel Hertz²¹ considered that true visceral pain occurs only in those lesions in which there is abnormal motor activity Interesting in this connection is Masson's¹ original suggestion in regard to neuromatous lesions—that they represented sympathetic neuromata enclosed in a double muscle layer, every contraction of these muscles forcibly compressing them He believed that if they contained neurites in communication with the appendiceal plexus, they may be a point of departure of more or less important reflex difficulties

To implicate the axial lesions in the tenderness elicited in these patients, one might best consider the tenderness as referred, a viscerosensory reflex, and accept the autonomic nerve fibers as the afferent paths for the transmission of stimuli arising in the appendiceal lesion While this evaluation would appear to be the logical one, we are reminded that the tenderness is evoked generally, by very deep palpation This may produce traction on the mesentery, and peritoneal irritation or by the compression of a tense viscus, splanchnic pain With reference to this we may recall a statement of Hertz²¹ that "referred pain, the result of the arrival in the spinal cord of impulses from an internal organ, is comparatively rarely present alone, as the impulses from the internal organ generally themselves give rise to visceral pain But pain originating in the peritoneum in connection with disease of the alimentary canal is not uncommon in the absence of visceral pain" To further obscure the situation one may recall another observation of this author²¹ that "visceral sensibility is exaggerated by training in hypochondriasis and visceral and referred sensations are exaggerated by the irritable condition of the central nervous system in neurasthenia and anemia"

Realizing the complexity of concepts of the origin of visceral pain, it seems evident why the presence of nervous elements in certain appendices has been linked with pain felt by the respective patients Though efforts have been made to establish a symptom complex fairly pathognomonic of neurogenic appendicitis (Hosoi,⁷ Llombart,¹⁰ Montandon,²⁶ Simard⁸), only a few investigators have satisfied themselves that such a symptom complex actually exists Urech,⁵ Montandon²⁶ and Schack¹³ definitely doubted the possibility of a preoperative diagnosis of neurogenic appendicitis being made While the histories of many patients having neuromatous lesions of the appendix may be suggestive, the objective findings are not too distinctive

In an attempt to evaluate the significance and faculties of these controversial lesions in the appendix, we accept the theory of Masson¹⁸ and Hill¹⁷ that the mucosa of the intestine contains sensory fibers and that these lesions represent exuberances of the same fibers (Masson)⁴ We will regard the pain and tenderness as mediated by the splanchnic nerves whose receptors we

will hypothetically place in the innermost portions of the appendix (mucosa or submucosa). Our purpose is to eliminate all other factors which might be accomplices to, or actual agents in, the production of symptoms.

Material and Methods—One hundred forty-three appendices showing neuromatous lesions and some degree of obliteration, encountered among the routine surgical specimens over a period of two years, were investigated. Because of the high incidence of neuromatous lesions in appendices showing some degree of obliteration, this study deals with such appendices. The organs were fixed in 4 per cent formalin, and paraffin sections from the base, midportion, and tip were stained with hematoxylin and eosin, and by the van Gieson, and the Masson trichrome silver stains. Of these appendices, 81 were removed with the preoperative diagnosis of appendicitis, 62 were removed simultaneously with gallbladders or female genital viscera. The vast majority of the lesions observed were argentaffin neuromata, instances of neuromuscular hyperplasia being relatively infrequent.

Conscious of the fact that failure to demonstrate the presence of neuromatous lesions may be the result of inadequate examination, but recalling that according to Masson¹ these nervous lesions may be ephemeral, as a control 36 appendices showing no neuromatous lesions and some degree of obliteration were investigated for their comparative value with appendices showing nervous lesions.

The clinical histories of all cases were analyzed with special attention to types of discomfort complained of, physical and laboratory findings, histories suggestive of previous discrete appendicular attacks and actual operative findings.

A short histologic description of the neuromatous lesions encountered in these 143 appendices shall be given. This is followed by a tabulated analysis of the histories of the various patients, whose appendices did or did not show neuromatous lesions, the histories of the latter being used as controls. An attempt to correlate the clinical and pathologic findings concludes the study. According to whether or not the appendix was the sole cause of the patient's discomfort, the material at our disposal was divided into three groups.

Group I deals with the histories and clinical findings of patients whose appendices, containing neuromatous lesions, were removed with the preoperative diagnosis of appendicitis. Special attention was given to the temperature, leukocyte counts, complaints, histories of previous attacks of appendicitis, and physical and operative findings. Group II deals with the histories and clinical findings of patients whose appendices, likewise removed with the preoperative diagnosis of appendicitis, disclosed no neuromatous lesions. Group III deals with patients having neuromatous lesions in incidental appendices, *i.e.* appendices removed routinely during cholecystectomy or gynecologic operations.

Pathologic Description—Lesions varying from mere streaks to diffuse or circumscribed masses of neuromatous tissue measuring up to 14 Mm. were encountered in 143 appendices. In a single appendix the varied con-

figurations of the axial lesions could be demonstrated. Thus one segment revealed the negligible lumen reduced to a small slit containing cellular detritus. The fragments of epithelium of opposing sides and three crypts were surrounded by masses of lymphocytes peripherally in distinct follicle arrangement. Lymphoid elements composed the mass of tissue between residual epithelium and peripheral submucosa. In a subsequent segment lumen and epithelium were absent. At the axis of a generally fatty submucosa were distinct or fusing nodes, composed of lacy tissue from which occasional strands penetrated adjacent tissue containing lymphocytes. In sections stained with hematoxylin and eosin, the lace-like tissue was composed of tortuous columns of vacuolated, lightly eosinophilic material, the columns outlined by denser eosinophilic threads. (With the Masson trichrome stain the lacy tissue appeared light, transparent, red or violet, the bordering fibers, dark blue.) Oval or spindle-shaped nuclei with diffusely distributed, fairly dense chromatin were scattered through the tissue generally in contact with the coarser eosinophilic threads. The impression was gained of columns of spongy tissue viewed in cross and tangential section. From the poles of these lesions outspoken strands of tissue emerged. In a third and more distal segment, the impression of strands was magnified by the closer distribution of thick eosinophilic threads, though here too the intervening stroma was vacuolated and outlined by delicate, darker red fibrils. In association with these were sometimes noted argentaffin cells. Argentaffin cells were likewise noted in lesions bordered by lymphocytes. In many cases the disposition of these lymphocytes in separated masses was distinctly reminiscent of the follicles of the mucosa and the submucosa. Other components frequently observed by us as well as by other investigators, were eosinophilic leukocytes. Both these elements are features of the normal mucosa. It seems that the lymphocytes, because of the frequent regularity of their disposition, are generally not evidences of regression of argentaffin neuromata but rather, like the neuromatous tissue, vestiges of the normal mucosa and submucosa.

In a few instances the light-staining elements were delicate columns or strands among which were ganglia cells. For the presence of these we postulate inflammation which, in completely destroying the mucosa or in producing cicatricial contraction in a centripetal direction, thrusts these submucosal structures, possibly irritated to hypertrophy, in a prominent and axial position.

Occasionally a nodule was seen which tinctorially very closely resembled in its constituents the muscularis mucosa, the columns or fibers in these cases being somewhat more compact. In a single instance the unobliterated segment disclosed a proliferation of muscularis mucosa with apparent extension into the mucosa. In the obliterated segment of another appendix, a circumscribed lesion measuring 0.45 Mm adjoined a cluster of lymphocytes. Though tinctorially somewhat lighter yellow, in sections stained by the van Gieson method, this lesion morphologically resembled the muscularis mucosa. In an unobliterated segment of the same appendix, the muscularis mucosa definitely and contrastingly bordered hyperplastic mucosal nerve elements. Throughout

the section nervous and muscular hyperplasia was observed, the nervous tissue being very conspicuous in the mucosa. The above represents the slightly varied pictures, exclusive of pure scar and granulation tissue, which we observed.

From this short outline it may be inferred that the structures described may be nervous elements. In morphology they strongly resembled the mucosal mesh. From our material it appears that the nerve tissue present in the center of obliterated appendices, just as the lymphocytes and lymph follicles which were often encountered, is an apparent vestige of elements normally present in the mucosa and submucosa of the appendix.

GROUP I

HISTORIES AND PHYSICAL FINDINGS IN PATIENTS WHOSE APPENDICES, CONTAINING NEUROMATA, WERE REMOVED WITH THE PREOPERATIVE DIAGNOSIS OF APPENDICITIS

Table I is included to show the pertinent data, particularly evidences of pain, tenderness, *etc.*, which could perhaps be interpreted as the result of neuromata.

Operative Pathology—The following are the pertinent features found at operation for removal of appendices which contained the neuromatous lesions and no evidence of inflammation.

Of the 51 partially obliterated appendices, 30 were kinked or adherent to neighboring viscera, 13 were fibrotic or atrophic but showed no peritoneal adhesions or inflammation. Eight were associated with other pathologic findings such as sliding inguinal hernia, marked retroversion of the uterus, distended cecum or hyperperistaltic ileum, mesenteric lymphadenitis, perisalpingitis, ruptured peptic ulcer, large ovarian cysts, and abscess of the liver.

Of the 13 patients showing no peritoneal adhesions, in whose appendices, according to our standards of elimination, neurogenic lesions would be acceptable as the etiologic element in the production of symptoms, one patient had, in addition to appendiceal symptoms, multiple complaints such as headache, constipation and arthritis. Another was operated upon during an attack similar to one experienced six months previously, a third during one of multiple attacks, some associated with fever and the first occurring two years previously. Three described multiple attacks associated with only appendiceal pain. Two described attacks associated with episodes of diarrhea and fever, and one with constipation. One patient complained of a loss of weight attributed to loss of appetite. The pain in another was provoked by hunger and relieved by food. Another, with no history of similar attacks, recalled epigastric distress, experienced one year previously and relieved by soda. The abdominal pain in another was related to menses.

Of the 21 obliterated appendices, eight showed peritoneal adhesions of some degree occasionally producing kinks. Nine were associated with extra-appendiceal alteration. Four disclosed fibrotic changes or were normal. Of the four showing neither peritoneal involvement nor mechanical alteration,

NEUROGENIC APPENDICES

TABLE I
APPENDICES CONTAINING NEUROMATOUS LESIONS

Some of the Pertinent Signs and Symptoms	Number of Patients with a Clinical Diagnosis of					Miscellaneous Diagnoses
	Acute Appendicitis	Subacute Appendicitis	Chronic Appendicitis	"Interval" Appendix	"Appendicitis"	
	17	15	16	23	7	3
Number of patients having pain in epigastrium	1	3	1		1	
Epigastrium and right lower quadrant	8		1	4		
Right lower quadrant	8	12	14	17	4	3
Lower abdomen					1	
Left lower quadrant					1	
Diffuse pain				1		
Number of patients having tenderness in epigastrium	2					
Epigastrium and right lower quadrant				2	2	
Right lower quadrant	13	12	16	12	3	3
Lower abdomen	1					
Left lower quadrant and hypochondrium				1	1	
Diffuse tenderness	1	1		1		
Number of patients having rigidity in right rectus region	9	2		3		1
Number of patients having gastro-intestinal disturbances						
Nausea	1	3	5	9	2	1
Vomiting						
Nausea and vomiting	3	5		4		
Diarrhea	1	1		2	1	1
Constipation	1			4	1	1
Nausea and diarrhea	1					
Elevation of temperature	16	4	2	3	1	
Increased white blood count	16	7	8	9	2	
Previous attacks	8	9	8	14	3	
Remarks						
Acute Appendicitis						
Five appendices showed histologic evidence of inflammatory lesions						
Six appendices associated with extra-appendiceal lesions						
Subacute Appendicitis						
One appendix showed histologic evidence of inflammation						
Two appendices associated with extra-appendiceal lesions						
Chronic Appendicitis						
One appendix showed histologic evidence of inflammation						
Three appendices associated with extra-appendiceal lesions						
"Interval" Appendix						
Two appendices showed histologic evidence of inflammation						
Four appendices associated with extra-appendiceal lesions						
Six patients disclosed no tenderness						
"Appendicitis"						
Two appendices associated with extra-appendiceal lesions						

in two patients the pain occurring in attacks was associated with episodes of constipation. Another, with a preoperative diagnosis of acute appendicitis, had a leukocyte count of 16,000, the urine postoperatively containing red blood

cells and occasional white blood cells. The fourth, a diabetic, complained of epigastric pain and belching of nine weeks' duration.

Summary—Eighty-one patients whose appendices, containing neuromata, were removed with the preoperative diagnosis of appendicitis, disclosed the following:

Protocols revealed that 42 patients had histories of previous discrete attacks, after which discomfort persisted for a period, or gave histories of definite recurrent attacks.

Of the 81 appendices, nine were the seat of inflammation, two showing acute suppurating inflammation, this condition having been diagnosed preoperatively. Two appendices displayed less extensive inflammations: one a catarrhal inflammation, the other a focal suppurating inflammation. Of these one was diagnosed acute appendicitis, the other "interval appendix."

Five showed subacute obliterating, or subacute inflammation in partially obliterated appendices. Two of these showed gross evidence of previous inflammation in the nature of periappendiceal adhesions. Of these five appendices, two were diagnosed preoperatively as acute appendicitis, one as an interval appendix, one as subacute, and the fifth as chronic appendicitis. All the patients gave histories of similar previous attacks. At the time of operation the temperature and leukocyte counts of four patients were normal. The fifth patient, operated upon with the diagnosis of acute appendicitis, had a slightly elevated temperature, a leukocyte count of 12,000, and some rigidity.

Thirty-eight appendices showed periappendiceal adhesions or bands producing kinking or stasis with fecoliths.

Seventeen patients had clinical evidence and operative confirmation of extra-appendiceal lesions.

The appendices of 17 patients were observed to be thickened, fibrotic or normal, with no record of extra-appendiceal involvement or impaction.

The ages of the patients in this group varied between ten and 52 years. Nine were in the second, 38 in the third, 12 in the fourth, 20 in the fifth and two in the sixth decades. Twenty-eight of these patients were men, 53 were women.

From an analysis of the histories and clinical findings, in the absence of any uniformity and specificity of signs or symptoms, it seems clear that the neuromatous elements in all these appendices cannot be made responsible for some of the symptoms and particularly for the pain suffered by these patients. These findings do not substantiate the correctness of the diagnosis "neurogenic appendicitis."

GROUP II

HISTORIES AND PHYSICAL FINDINGS OF PATIENTS WHOSE APPENDICES, CONTAINING NO NEUROMATA, WERE REMOVED WITH THE PREOPERATIVE DIAGNOSIS OF APPENDICITIS

Table II shows the pertinent data, particularly evidences of pain, tenderness, etc., in a series of patients upon whom the clinical diagnosis of appen-

ditis was made. These appendices showed no neuromata. This group may serve as a control to determine whether or not symptoms and physical findings, particularly in regard to pain and tenderness, differ in patients with and without appendiceal neuromata.

TABLE II
APPENDICES CONTAINING NO NEUROMATOUS LESIONS

Some of the Pertinent Signs and Symptoms	Number of Patients with a Clinical Diagnosis of				
	Acute Appendicitis	Subacute Appendicitis	Chronic Appendicitis	"Interval" Appendix	"Appendicitis"
	9	9	10	4	4
Number of patients having pain in epigastrium and right lower quadrant	2			1	
Right lower quadrant	4	7	7	3	4
Right upper quadrant	1	1	1		
Diffuse pain		1	2		
Number of patients having tenderness in epigastrium and right lower quadrant				1	
Right lower quadrant	7	8	6	3	4
Right upper quadrant			1		
Diffuse tenderness		1	1		
Number of patients having rigidity in right rectus region	4	1	1		
Number of patients having gastro intestinal disturbances					
Nausea	1		3		1
Vomiting and diarrhea		1			
Nausea and vomiting	3	2	2		
Diarrhea		2	1		1
Constipation		2	1		1
Elevation of temperature	9	3		1	1
Increased white blood count	9	4	2	1	
Previous attacks	4	7	8	4	
Remarks					
Acute Appendicitis					
Four appendices associated with extra-appendiceal lesions					
Subacute Appendicitis					
One appendix associated with extra-appendiceal lesion					
Chronic Appendicitis					
One appendix showed histologic evidence of inflammation					
Two appendices associated with extra-appendiceal lesion					

Operative Pathology—Of the 36 appendices showing no neuromatous lesions, a partially obliterated appendix was the seat of a subacute inflammation, the temperature and white blood count being normal. Of the 20 partially obliterated appendices showing no inflammatory lesions, in 12, factors were disclosed operatively which on a mechanical basis might have produced the

symptoms complained of. In three instances extra-appendiceal intra-abdominal lesions were disclosed operatively. In five no intra-abdominal or intrinsic appendiceal alteration was detected operatively, other than fibrosis.

Of the latter, three appendices were removed during one of frequent attacks of pain simulating appendiceal colic. The attacks in the fourth patient occurred premenstrually. In the fifth patient appendiceal symptoms were associated with belching and epigastric distress.

Six of 15 obliterated appendices disclosed at operation alterations which may have been responsible, on a mechanical basis, for symptoms. Extra-appendiceal lesions were associated in four instances.

Of the five showing neither intra-abdominal nor appendiceal alteration other than fibrosis, one was associated with postprandial pain and intractable constipation, another with diarrhea associated with emotional upsets, the pain of a third, originally unrelated to foods or evacuation, lately occurred postprandially and was associated with diarrhea, the fourth had recently sustained a deliberate (dietary) weight loss of 50 pounds, the fifth, operated upon with a diagnosis of acute appendicitis, had an elevation of temperature of 105°F and a white blood count of 12,500.

SUMMARY—Of 36 patients whose appendices, containing no neuromatous lesion, were removed with the preoperative diagnosis of appendicitis, 23 gave histories of previous discrete attacks simulating appendicitis. One appendix was the seat of subacute appendicitis. Eighteen appendices showed peri-appendiceal adhesions. Extra-appendiceal lesions were present in seven instances. Ten appendices were thickened, fibrotic or normal but disclosed no extrinsic lesions. The ages of the patients in this group varied between 11 and 62 years, 30 being evenly distributed in the second, third and fourth decades, six patients being above 41 years of age. Eight patients were men, 28 were women.

From an analysis of this control group, it seems clear that the histories and clinical findings of these patients did not vary greatly from those whose appendices contained neuromata. This fact also makes the diagnosis "neurogenic appendicitis" very questionable.

GROUP III

INCIDENTAL FINDINGS OF NEUROMATOUS LESIONS IN APPENDICES WHICH WERE REMOVED DURING CHOLECYSTECTOMIES, HYSTERECTOMIES, ETC

This group may be mentioned in passing only. It also may serve as control to show pertinent signs and symptoms obviously related to the main disease, in instances in which the appendices just happened to show neuromata.

Thirty-one appendices with neuromatous lesions accompanied diseased gallbladders. The symptomatology and objective findings in these patients were entirely related to gallbladder disease. The tenderness was largely restricted to the hypochondrium and the right upper quadrant. The neuromatous lesions

varied up to 0.375 Mm in diameter. Areas in the mucosa of the unobliterated portions frequently contained prominent nervous elements. Of interest is the fact that patients in this group varied in age between 26 and 59, the majority being in the fourth and fifth decades. There were 26 women and five men.

Of 31 appendices containing neuromatous lesions, 21 accompanied large uterine myofibromata, many with adenomyosis. Four accompanied large ovarian tumors, one an inflamed salpinx, one an ectopic pregnancy, and one a ruptured ovarian cyst. Three accompanied wedges of ovarian tissue excised because of multiple follicle cysts. The ages of the patients varied between 13 and 57, 17 being in the fifth decade, seven in the fourth.

Twenty-three patients had alterations in menses. Seventeen complained of pain usually in the lower abdomen. No tenderness was elicited in 12 instances. A mass was palpated without the production of tenderness in three and with production of tenderness in four patients. Ten patients evidenced tenderness to abdominal or vaginal palpation. Tenderness in the right lower quadrant was elicited in only two patients, one having a tubal pregnancy, the other a recently ruptured ovarian cyst.

Twenty-nine patients were operated upon with a gynecologic diagnosis, two with diagnoses of appendicitis. One of these actually had a ruptured ovarian cyst, the other, a salpingitis.

Discussion—A rigid analysis of the histories and operative findings in 81 patients whose appendices showed neuromatous lesions and some degree of obliteration, revealed nine appendices to be the seat of inflammation, 17 to be associated with extra-appendiceal lesions and 38 with peritoneal adhesions or bands. Whereas these adhesions did not always involve attachment to the parietal peritoneum or mesentery and irritations of somatic nerves, they definitely introduced a barrier to the proper functioning of the intestine. It is our impression that the symptoms of appendicitis occurring in repeated attacks at varying intervals may primarily have a mechanical basis. The kinking, twisting or fixation of the appendix, by adhesions or bands, may interfere with its property of evacuation. This failure to empty may produce intermittent distention in an already thickened or poorly distensible organ, producing pain without elevation of temperature and leukocytes, a syndrome frequently diagnosed as "chronic appendicitis," or "interval appendicitis." If, however, this failure to empty produces prolonged stasis and possible interference with circulation, an inflammation may supervene. This inflammation may be severe or mild, obviously demanding surgical intervention, or subsiding spontaneously, leaving as evidence more adhesions, further kinking, and denser fibrosis. When the appendix is entirely obliterated, the element of distention in the production of pain is not a consideration. However, there is roentgenologic evidence that periappendiceal adhesions causing a tug on neighboring segments of intestine may alter the normal evacuation of the ileum and probably incite some degree of distress.

Seventeen appendices satisfied our criteria, in that mechanical and ex-

trinsic factors were eliminated. However, comparisons of these with appendices likewise devoid of extrinsic alterations and showing no neuromatous lesions somewhat weakened their significance. Sixty-two appendices removed simultaneously with other organs, the major seat of pathologic changes, and being associated with no, or rare and questionable appendiceal symptoms, disclosed neuromatous lesions of comparable magnitude. The apparently incidental feature of the lesions in these instances and the fact that they occurred at a relatively advanced age further detract from their specificity.

In several well studied cases, fortuitously occurring in physicians or their relatives, neuromatous lesions were encountered in the obliterated portion of acutely inflamed appendices, and histories of multiple very similar, perhaps less severe attacks than that provoking the operation, were obtained. In the course of examination of appendices accompanying other organs, often catarrhal, sometimes focal suppurating inflammation is encountered, actually an accidental finding. That appendicitis of subclinical variety may occur is evidenced by our still high mortality from appendicitis. That relatively benign inflammations occur and subside is manifest by the high percentage of obliteration encountered in age groups incompatible with involutional obliteration of the appendix. However, the presence of the same lesions in older age groups as disclosed by the 62 appendices accompanying diseased gallbladders and internal genital organs, would indicate them to be merely a feature of obliteration.

If the lesions are the sequelae of inflammation, they may be products of precipitous alterations of the mucosa. Inflammation notoriously depletes the lymphoid tissue (Masson¹⁸), leaving the residual mucosal elements conspicuous. Of these, nerve fibers are a prominent component. Opposing portions of residual mucosa and submucosa at the site of injury fuse and thus we obtain the picture illustrated by many authors of neuromatous lesions of the appendix. Masson stated that neuromata in the state of regression are infiltrated by lymphocytes, and distinguished between infiltrating lymphocytes and persistent follicles. It has been our experience to find large neuromatous lesions bordered or separated by lymphocytes, very frequently in follicle formation, to find infiltrating lymphocyte coextensive with outspoken follicles. We have the impression that the presence of lymphocytes is not a reliable evidence of regression of neuromata and that these cells are most frequently residual elements of the mucosa or submucosa.

The histories of patients with and without neuromatous lesions vary little. Specific characters are lacking, particularly as concerns pain. It is neither more confined to one region, nor more diffuse, neither more nor less severe in those patients with neuromatous lesions in their appendices, than in patients without such appendiceal lesions. This is also true when the appendix shows inflammatory changes in addition to neuromatous lesions. From the histories of the patients with neuromata in their appendices, and from the histories of the control groups, it seems clear that the neuromatous lesions in the appendix

are mere incidental findings, not likely either to cause clinical symptoms or to alter the clinical symptoms of any variety of appendicitis. The term "neurogenic appendicitis," therefore, seems unwarranted.

CONCLUSIONS

The so-called neuromatous lesions occurring in the axis of a considerable percentage of partially or completely obliterated appendices appear to be remnants of mucosa, entangled in obliterating fibrous connective tissue. When noted in young adults, they are perhaps stigmata of previous inflammatory assault upon the mucosa or submucosa.

Appendices containing no neuromatous lesions, used for clinical comparison, disclosed very similar clinical histories and operative findings.

By a process of elimination, only fragmentary evidence of the implication of these in the clinical phenomena of "chronic appendicitis" was obtained.

These neuromatous structures in young individuals might be regarded as evidence of previous attacks of appendicitis, but are certainly of questionable value from a differential clinical diagnostic standpoint.

From the facts at our disposal, it does not seem likely that a clinical diagnosis of neurogenic appendicitis can be made.

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THE INFLUENCE OF THE EXTERNAL SECRETION OF THE PANCREAS ON LIPID METABOLISM*

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It has long been known that in diabetes mellitus a disturbance of the metabolism of both fats and carbohydrates may occur. Because the two phenomena seemed to be interrelated it was not unnatural that, when insulin was discovered, students of the subject rather generally assumed a wholly adequate replacement therapy had been found. That such is not the case, in certain respects at least, was soon noted by Allan, Bowie, Macleod and Robinson¹ (1924). These workers found in completely depancreatized dogs, in which the carbohydrate metabolism was controlled by insulin, that when life was prolonged for a sufficient length of time, a disturbance in lipid metabolism developed which was characterized by the deposition of excessive amounts of fat in the liver. This observation has been amply confirmed from other laboratories.

Much later, in 1937, Kaplan and Chaikoff² established that the process is a slow and variable one and that dogs fed a low fat diet plus vitamin and salt supplements usually require at least 16 weeks to insure the consistent finding of a fatty acid content in excess of 14 per cent of the wet weight of the liver.† These authors³ also noted following pancreatectomy in animals controlled with insulin, that a quite prompt and persistent fall occurs in the blood lipid levels which is most marked for free and esterified cholesterol. Indeed, cholesterol ester was found at times to have disappeared from the blood stream.

It is especially interesting that Allan and his coworkers,¹ after having discovered the fatty liver phenomenon, also found the means for its control. This consists of the administration of raw pancreas. Later, Hershey and Soskin⁴ observed that lecithin also is effective, and Best, Ferguson, and Hershey⁵ reported that the potent agent in lecithin is choline. Ralli, Flaum, and Banta⁶ confirmed the value of lecithin, and noted that when the animal was fed fat, lecithin was less effective than raw pancreas, but that when the diet was low in fat lecithin was somewhat more effective. Then Dragstedt, van Prohaska, and Haims⁷ reported that the adequate dose of raw pancreas

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† The average normal fat content of the liver varies between 3 and 5 per cent of wet weight.

contains far too little choline for the latter to be responsible for the beneficial results obtained. They also noted certain other phenomena which led them to conclude that a new fat-controlling hormone had been discovered. Their observations and reasoning briefly stated are

(1) Total pancreatectomy in animals maintained with insulin is followed by fatty infiltration of the liver

(2) Choline and raw pancreas prevent and cure the process, but the effective dose of the latter contains far too little choline for this substance to be the potent agent of the gland

(3) The effective factor in raw pancreas is not an enzyme carried by the external secretion, since (a) Exclusion of the pancreatic juice from the intestine either by draining it to the outside through a fistula or by ligating the pancreatic ducts does not cause the disorder, and (b) the feeding of fresh pancreatic juice to the depancreatized dog in amounts of from 100 to 1,000 cc per 24 hours, for from 24 to 142 days, does not prevent fatty livers from developing

(4) The effective factor can be isolated by an alcoholic extract of raw pancreas and probably is a hormone

The hormone hypothesis has not yet been proved, however. Even before the work of Dragstedt, *et al*^{7a, b} appeared, the literature contained data which are directly opposed to certain of the findings upon which their conclusions are based. Reference is made specifically to the deposition of fat in the liver following the exclusion of the external secretion of the pancreas from the intestine. In 1905, Pfluger⁸ observed that when dogs were subjected to subtotal pancreatectomy and to ligation of the pancreatic ducts, a great increase in the liver fat supervened. These data can be criticized on the grounds that the subtotal pancreatectomy may have created an islet tissue insufficiency which was responsible for the fatty livers. Such criticism cannot be applied to the work of Berg and Zucker⁹ who reported, in 1931, that when pancreatic juice was drained to the outside by fistula or when the pancreatic ducts were effectively ligated, extensive fatty infiltration of the liver developed. Moreover, careful analysis of the data presented by Dragstedt, *et al*, suggests that significant changes may have been misinterpreted. They report that three dogs were subjected to duct ligation and kept on a lean meat, whole milk, and bread diet apparently without vitamin supplements and that the animals lost weight rapidly and died in 44, 56, and 83 days, respectively. At autopsy, the pancreas was extensively degenerated, but some acinar tissue, as well as the islets, was preserved. Histologic sections of the liver showed slight fatty infiltration in two cases, but in the third the liver was entirely normal. It is not certain that these authors were justified in passing over the slight lipid infiltration as of no significance, since the time of survival was less than 14 weeks and since it has been shown more recently by Rall, Rubin, and Present,¹⁰ using chemical analysis, that successful ligation of the pancreatic ducts in three dogs that were observed for from 13 to 15 weeks resulted in fatty changes in the liver of each one

which were indistinguishable from those seen in the completely depancreatized dog. At the time the work of Rall and her collaborators appeared, Chaikoff, Entenman and I^{11a b c} were studying the same subject. We confirmed their findings on a larger series of animals. We also made observations on the

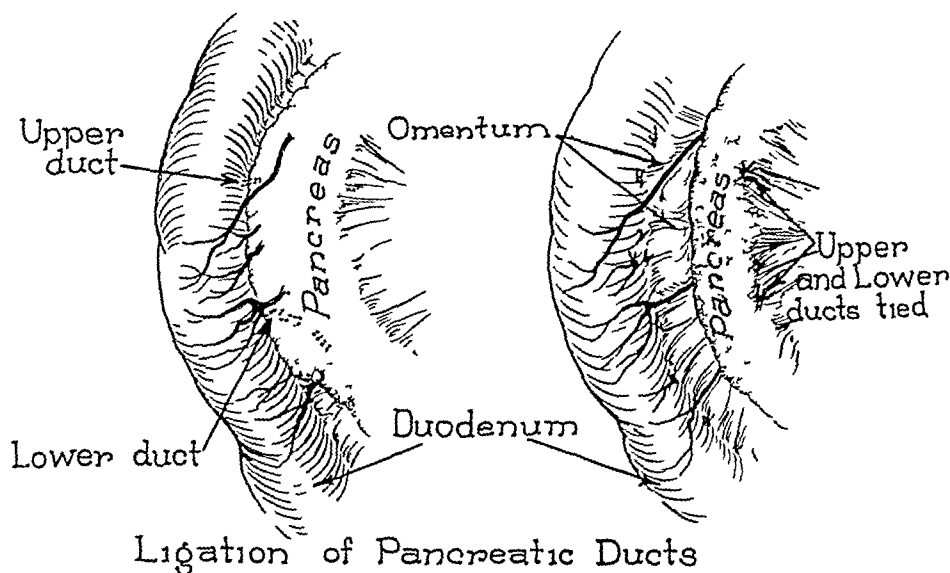


FIG. 1.—Diagrammatic drawing showing the operative procedure

effect of ligation of the pancreatic ducts upon the blood lipid levels and studied the influence of the feeding of pancreatic juice upon the blood and liver lipids of the depancreatized dog, maintained with insulin, and of the dog subjected to ligation of the pancreatic ducts. Representative portions of the experimental data are presented here in four sections.

EXPERIMENTAL STUDIES

(I) The Effect of Ligation of the Pancreatic Ducts upon Liver and Blood Lipids

Procedure—The two main pancreatic ducts were doubly ligated and divided between the ligatures. The proximal stumps were then pulled through the gland and tied to the mesentery on the antiduodenal side. All nervous and not definitely identifiable connections between the pancreas and duodenum were severed, including the smaller blood vessels, so that there was no possibility of a ductal communication remaining. Finally, the space between the gland and the duodenum was filled in with omentum which was sutured to the bowel (Fig. 1).

The animals were kept on a low fat, adequate vitamin supplement, and salt mixture diet both before and after the operation and blood samples were taken at frequent intervals. Fasting blood sugars were determined repeatedly upon these animals. With the exception of Dog E20, the values fluctuated between 62 and 92 mg. per cent. Blood sugar levels of from 75 to 82 mg. per cent were found in Dog E20 during the first nine weeks after duct

ligation A day prior to removal of the liver this dog showed a fasting blood sugar of 127 mg per cent The animals were sacrificed after 20 to 24 weeks had elapsed, or earlier if a fatal termination seemed imminent, and the liver and pancreas were examined The liver was weighed and passed through a meat chopper three times to insure thorough mixing This procedure was employed to make sure that the sample to be analyzed would reflect the average for the entire liver, since Chaikoff and Kaplan¹² have shown in the depancreatized dog maintained with insulin that the deposition of fat may vary considerably in the different lobes of the same liver The methods used for analysis have been described elsewhere (for blood³, for the liver¹³)

The study was divided into three parts First, nine animals were fed the basic diet only, second, four animals were given the basic diet and eight units of insulin twice daily, third, six animals were fed the basic diet plus 125 Gm of raw pancreas twice daily

Results—Autopsy showed in the 19 animals that duct ligation had been successful, as represented by atrophy of all recognizable acinar tissue A variable amount of islet tissue was observed in the different animals In general, it was considerable and was found chiefly in the proximal or gastric one-third of the pancreas Some islet nodules also were evident in the distal one-third, while the central one-third was represented by a dense fibrous tissue surrounding the blood vessels which showed no gross evidence of islet structures

Fatty infiltration of the liver, when present in any sizeable amount, was easily recognized, grossly, by the yellowish, mottled appearance of the peritoneal and cut surfaces of the organ

Group 1—Basic Diet Only The animals were studied for from 12 to 24 weeks, with an average of 18 weeks All of them lost weight, despite the fact that their appetites were good and that they ingested more food than is usual for animals of their size Repeated fasting blood sugars were taken and showed a range between 62 and 92 mg per cent With only one exception the liver cholesterol and fatty acids showed marked elevations above the normal The fatty acids ranged between 11.4 and 35.5 per cent, compared with the normal of from 3 to 5 per cent The one exception (Dog E23) had a high cholesterol content (0.51 per cent compared with normal of 0.25 per cent), but a relatively normal fatty acid figure of only 2.67 per cent (Table I) The reasons for this variation are not clear, although time may have been a factor, since the animal was sacrificed 13.5 weeks after operation On the other hand, the blood lipid changes in this animal were not different from those observed in the other animals

The blood lipid findings were rather variable, but in general they showed a distinct fall in all lipid constituents with the drop in esterified cholesterol being the most marked Thus, the blood and liver lipid changes in the duct-ligated animal correspond with those found by Chaikoff and Kaplan^{3, 13} in the completely depancreatized dog maintained with insulin

Group 2—Basic Diet Plus Eight Units of Insulin Twice Daily Three animals were studied for 20 weeks and one for 16 weeks Their appetites

TABLE I
BLOOD AND LIVER LIPIDS OF DUCT-LIGATED DOGS MAINTAINED ON A LIVER MEAT DIET (WITH OR WITHOUT SUCROSE)*

Dog No	Period after Duct Ligation	Weight	Cholesterol				Total Fatty Acids	Phospho lipid	Total Lipid	Resid unligated Fatty Acids	Period Mean after Duct Ligation	Liver Weight	Total Cholesterol	Total Fatty Acids	Phospho lipids	Diet [†] Sucrose	Condition, End of Period of Observations
			Total	Free	Ester												
Weeks	K ₅	Mg per 100 cc	Mg per 100 cc	Mg per 100 cc	Mg per 100 cc	Mg per 100 cc	Mg per 100 cc	Mg per 100 cc	Mg per 100 cc	Mg per 100 cc							

L7	Before (o)	11 6	No studies made																			
L9	Before (o)	8 0	No studies made																			
L12	Before (o)	5 8	No studies made																			
L13	Before (o)	8 4	156	136	20	482	350	638	232	21	370	0 66	29 0	1 41	250	50	Good nutritional state					
L20	Before (o)	8 4	88	88	0	243	195	331	112													
L23	Before (o)	8 4	111	82	29	173	170	284	38													
L29	Before (o)	11 2	109	109	2	284	252	395	114													
L31	Before (o)	10 5	138	107	31	388	360	526	124													
L34	Before (o)	10 5	78	78	0	234	226	312	83	14 5	290	0 41	11 5	2 04	250	50	Weak					
L34	Before (o)	11 5	129	110	19	235	227	364	69													
L34	Before (o)	11 5	170	125	45	400	350	570	132													
L34	Before (o)	11 5	177	131	46	392	330	560	136													
L34	Before (o)	9 2	114	113	1	214	203	328	77	12	510	0 32	35 5	1 93	305		Very weak and emaciated					
L23	Before (o)	7 0	81	71	10	210	187	291	78													
L23	Before (o)	6 6	94	82	12	225	169	319	103													
L23	Before (o)	15 2	156	132	24	380	335	536	138													
L23	Before (o)	15 3	149	122	27	362	330	511	120													
L29	Before (o)	5 5	10 1	133	25	383	316	521	153													
L29	Before (o)	6 7	82	81	0	201	232	343	106	13 5	140	0 51	2 67	2 48	350		Very weak and emaciated					
L29	Before (o)	13 5	6 7	85	10	246	195	331	108													
L29	Before (o)	10 5	170	142	28	410	400	580	121													
L31	Before (o)	9 1	145	126	19	318	282	463	118													
L31	Before (o)	8 8	145	125	4	361	292	471	115													
L31	Before (o)	8 5	145	125	0	264	280	409	73													
L31	Before (o)	8 4	115	119	4	272	242	387	110	18 5	220	0 31	17 7	2 06	252		Good condition					
L31	Before (o)	15 8	177	142	35	522	398	699	229													
L34	Before (o)	11 4	144	135	15	315	302	450	102													
L34	Before (o)	10 3	101	101	1	210	234	414	52													
L34	Before (o)	12 8	113	112	8	266	212	367	124													
L34	Before (o)	9 3	117	109	0	270	224	387	127	18 5	300	0 42	20 6	1 79	362		Very weak at end					
L34	Before (o)	8 1	98	100	0	292	224	390	142													
L34	Before (o)	11 1	193	141	52	351	416	544	34													
L34	Before (o)	8 0	118	118	0	262	265	380	84													
L34	Before (o)	6 8	90	66	24	193	183	283	53													
L34	Before (o)	5 1	110	94	16	340	260	450	154	16	255	0 36	19 6	1 84	295		Extremely weak and emaciated					
L34	Before (o)	5 0	130	83	17	313	260	443	105													

*Completeness of ligation of ducts confirmed at necropsy
† The figures in parentheses show the number of days prior to duct ligation when preoperative bloods were taken. Preoperation diets in Tables I to III consisted of 30 Gm. of lean meat per kilo. 6 Gm. of sucrose per kilo per day, with the addition of vitamin and salt supplements.
‡ Constituents, in amounts recorded, were fed twice daily after duct ligation, at 8 A.M. and 4 P.M. Vitamin supplements were added either daily or twice weekly. Two Gm. of Cowgill's salt mixture were added daily.
§ All the dogs had good appetites throughout the period of observation.

* Completeness of ligation of ducts confirmed at necropsy.
[†] The figures in parentheses show the number of days prior to duct ligation when preoperative bloods were taken. Preoperative diets in Tables I to III consisted of 30 Gm of lean meat per kilo 6 Gm of sucrose per kilo per day, with the addition of vitamin and salt supplements.
[‡] Constituents, in amounts recorded, were fed twice daily after duct ligation, at 8 A.M. and 4 P.M. Vitamin supplements were added either daily or twice weekly. Two Gm of Cow-Milk salt mixture were added daily.
[§] All the dogs had good appetites throughout the period of observation.

TABLE II
BLOOD AND LIVER LIPIDS OF DUCT LIGATED DOGS MAINTAINED WITH INSULIN AND LEAN MEAT SUCROSE DIET*

Dog No †	Period after Duct Ligation ‡	Weight Kg	Blood Lipids							Period after Duct Ligation	Liver Weight Gm	Liver Lipids			
			Cholesterol			Total Fatty Acids		Phospho lipid Mg per 100 cc	Total Lipid Mg per 100 cc			Residual Fatty Acids Mg per 100 cc	Total Cholesterol Per Cent	Fatty Acids Per Cent	Phospho lipids Per Cent
			Total Mg per 100 cc	Free Mg per 100 cc	Ester Mg per 100 cc										
E21	Before (7) ‡	5 0	190	135	55	348	325	538	91	20	255	0 28	14 7	1 60	
	Before (0)	5 0	188	130	58	322	300	510	79						
	6	5 7	124	122	2	289	250	413	121						
	13	6 5	132	132	0	304	258	436	131						
	18 5	6 9	137	136	1	400	309	537	192						
E22	19	6 7	131	119	12	306		437		20	275	0 39	20 4	1 69	
	Before (7)	5 0	190	137	53	440	400	630	133						
	Before (0)	5 0	192	141	51	438	392	630	139						
	6	5 3	134	118	16	326	296	460	116						
	13	5 5	135	137	0	358	300	443	157						
E25	18 5	5 6	122	121	1	291	280	413	102	20	470	1 03	34 2	1 85	
	19	5 6	111	111	0	295	230	406	141						
	Before (0)	9 0	173	129	14	389	222	562	208						
	5	8 1	128	134	0	420	261	548	245						
	12	8 0	132	134	0	345	351	477	109						
L30	17 5	7 5	145	144	1	370	300	515	168	20	185	0 32	6 32	1 98	
	18	7 6	126	122	4	334	238	460	172						
	Before (5)	13 5	168	135	33	452	284	620	238						
	Before (0)	13 5	175	140	35	472	300	647	245						
	15	12 5	139	133	6	220	258	359	43						
	16	12 3	142	136	6	230	221	372	78	16					

* Completeness of ligation of the ducts was confirmed at necropsy. All animals recorded received eight units of insulin twice daily immediately after the ingestion of the diets. Their appetites were good throughout and they were all in good nutritional state during the entire period of observation.

† Dogs L21, E22 and E25 received twice daily 250 Gm of lean meat, 25 Gm of sucrose and 7 Gm of bone ash after duct ligation. Vitamin supplements were added twice weekly. Dog E30 received the same amounts of lean meat, bone ash and vitamin supplements but the amount of sucrose fed was varied from 25 to 50 Gm daily.

‡ The figures in parentheses show the number of days prior to duct ligation that preoperative bloods were taken.

TABLE III
BLOOD AND LIVER LIPIDS OF DUCT-LIGATED DOGS, MAINTAINED ON A LEAN MEAT-RAW PANCREAS DIET*

Dog No	Period after Duct Ligation†	Weight	Blood Lipids										Period Maintained after Duct Ligation	Liver Weight	Liver Lipids				Duct	
			Cholesterol					Phospho-lipid							Total Choles-terol	Total Fatty Acids	Phospho lipids	Lean Meat§	Rat Pan-creas	
			Total	Free	Ester	Total Fatty Acids	Mg per 100 cc	Mg per 100 cc	Mg per 100 cc	Mg per 100 cc	Mg per 100 cc	Mg per 100 cc								
E15	Weeks	Kg	Mg per 100 cc	Mg per 100 cc	Mg per 100 cc	Mg per 100 cc	Mg per 100 cc	Mg per 100 cc	Mg per 100 cc	Mg per 100 cc	Mg per 100 cc	Wks	Gm	Per Cent	Per Cent	Per Cent	Gm	Gm		
	Before (7)†	17 7	185	130	55	370	358	555	90											
	Before (6)	17 7	188	117	71	390	326	578	120											
	8 5	17 4	203	140	63	470	405	673	153											
	13	17 9	187	140	47	546	437	733	219											
E17	Before (7)	20	201	159	42	505	484	706	150			20	345	0 24	1 87	1 82	265	125		
	Before (6)	9 0	210	146	64	422	412	632	99											
	8	9 0	203	152	51	465	415	608	150											
	12	8 3	198	149	49	460	378	658	171											
	18 5	8 9	182	156	26	430	427	612	123			20	220	0 25	2 28	2 18	135	125		
E19	Before (5)	7 8	175	125	50	432	402	607	125											
	Before (6)	6	174	124	50	428	400	612	123											
	13	7 5	206	159	47	480	382	686	190											
	19	8 0	176	139	37	456	374	632	179											
	10	8 5	177	141	36	453	345	630	172			20	220	0 26	3 10	2 71	117	125		
E24	Before (7)	10 5	180	148	32	450	380	630	172											
	Before (6)	5	177	136	42	421	371	598	146											
	13	11 2	178	141	36	506	339	684	248											
	19	9 5	208	164	44	491	396	699	193											
	10	9 7	170	154	16	412	406	582	128											
E28	Before (6)	20	163	152	11	400	394	563	128			20	270	0 27	2 84	2 78	157	125		
	6	8 9	140	115	25	342	327	482	105											
	12	8 1	122	112	10	408	—	530	—											
	18	8 1	163	138	25	361	327	524	124											
	20	7 9	130	113	17	366	332	496	138											
E33	Before (6)	20	148	140	8	386	340	534	152			22	270	0 23	2 90	2 55	133	125		
	21	8 3	145	136	9	407	331	552	178											
	14 4	15 3										285	0 24	3 49	2 33	215	125			
	20																			

No studies made

* All dogs were in good nutritional state during period of observation, appetites good throughout. Completeness of ligation of ducts confirmed at necropsy.

† The figures in parentheses show the number of days prior to duct ligation that preoperative blood samples were taken.

‡ The constituents listed were fed twice daily. Vitamin supplements and 2 Gm of Cowgill's salt mixture were added daily. Each dog received approximately 25 cc of cod liver oil and 30 cc of the vitamin B concentrate per week.

§ Amount of lean meat given was based upon initial weight of dog. 30 Gm of lean meat per kilo per day.

were good and the volume of food ingested was large. In contrast to Group 1, two of the animals actually gained in weight, while the other two lost only a moderate amount of weight. Three of the four animals had marked increases in the total fatty acids of the liver which ranged between 14.7 and 34.2 per cent. The fourth animal (Dog E25) had a slight but distinct rise in the liver fatty acids above normal (6.32 per cent). The liver weight also was low. The blood lipids of this animal, however, were characteristic of the group. All four dogs showed a distinct tendency for the blood lipid levels to fall below normal. This was most marked for the esterified cholesterol (Table II). The findings were in all respects comparable with those of Group 1.

It is evident, then, that lack of insulin or loss of weight is not responsible for the lipid changes in the blood and liver of the dog subjected to successful permanent obstruction of the pancreatic ducts.

Group 3 —Basic Diet Plus 125 Gm. of Raw Pancreas Twice Daily. Five animals were kept for 20 weeks and one for 22 weeks. Three showed definite increases in weight and three very slight losses as compared with the preoperative level. The liver lipids remained low with fatty acids ranging between 1.87 and 3.49 per cent and total cholesterol between 0.23 and 0.27 per cent. The blood lipids were maintained at normal or near normal levels (Table III).

These findings correspond closely with the results obtained by Chaikoff and Kaplan¹⁴ for the completely depancreatized dog maintained with insulin and fed raw pancreas. They suggest that the blood and liver lipid changes which are demonstrable in the completely depancreatized dog maintained with insulin are due to the exclusion from the body of a substance produced by the acinar tissue or some other element of the pancreas which is removed by pancreatectomy and rendered ineffective by the changes which occur in the gland following successful ligation of the ducts. The recent studies of Montgomery, Entenman, Gibbs, and Chaikoff,^{15a} Montgomery, Entenman, Chaikoff, and Nelson,^{15b} and Entenman, Montgomery, and Chaikoff^{15c} point more directly to the pancreatic juice as the controlling medium. This work showed that the feeding of pancreatic juice to the duct-ligated dog and to the depancreatized dog, maintained with insulin, under the conditions employed, prevents the fatty infiltration of the liver and the fall in blood lipid levels which occur quite uniformly in the untreated controls. The data are summarized briefly in Sections II, III, and IV.

(II) The Effect of the Feeding of Fresh Unactivated Pancreatic Juice upon the Blood Lipid Levels of the Completely Depancreatized Dog Maintained with Insulin

The initial work was undertaken with the idea of determining whether the feeding of pancreatic juice would have an effect upon the blood lipids similar to the administration of raw pancreas.

Procedure —Pure, unactivated pancreatic juice was collected by means of a modified Elman-McCaughan fistula¹⁶ from dogs which were kept in a good

nutritional state by the feeding of an adequate diet containing vitamin supplements and 30 to 50 Gm of raw pancreas daily*. The salt losses were controlled by the addition of sodium chloride or sodium bicarbonate to the diet or by the intravenous administration of normal salt or Ringer's solution

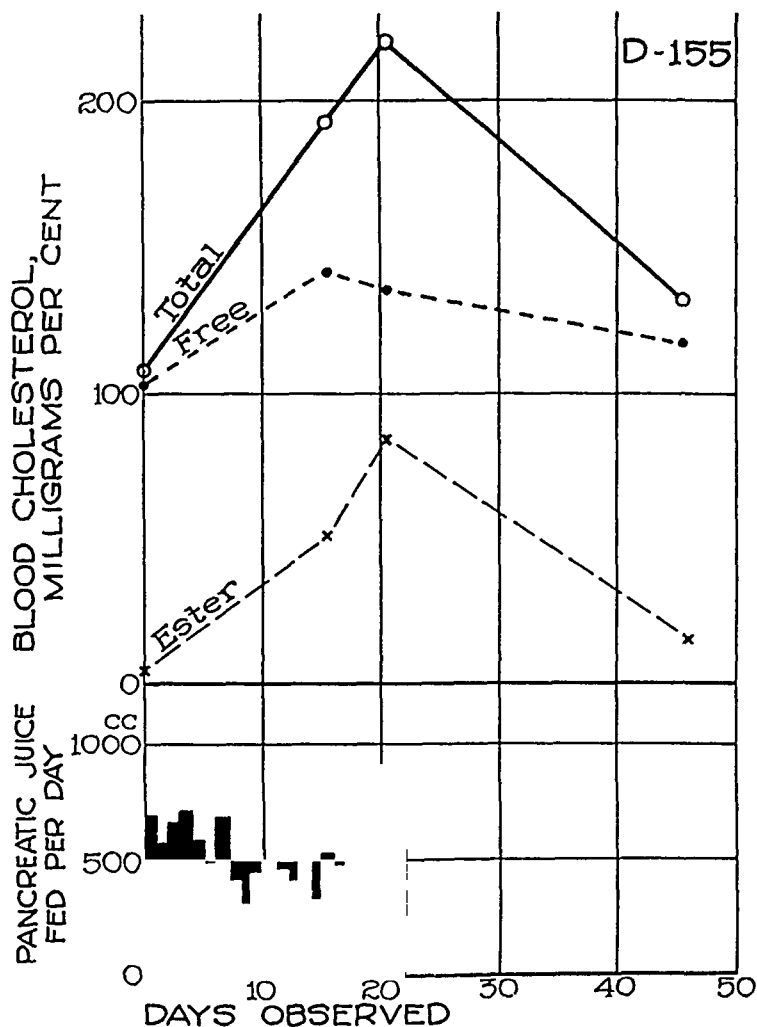


CHART 1—Showing changes in the blood cholesterol levels of the completely depancreatized dog maintained with insulin, in response to the feeding of fresh, unactivated pancreatic juice

The fresh juice was then thoroughly mixed with a basic diet consisting of raw lean meat, sucrose, bone ash, and vitamin supplements, and fed to the depancreatized dogs. Feedings, and eight units of insulin were given twice daily. The amount of juice fed ranged between 300 and 900 cc each 24 hours for a period of three weeks. Fasting blood samples were taken before, during, and after the pancreatic juice feeding period, and were analyzed by the chemical methods previously noted³. Four experiments were performed upon three dogs.

Results—In each experiment the blood lipids showed, initially, the low levels which are characteristic of the depancreatized dog³. Feeding of fresh pancreatic juice caused a prompt rise of these levels to or distinctly above normal. Withdrawal of the pancreatic juice resulted in a rapid return of

* The juice producers used in the longer experiments received 100 Gm of raw pancreas twice daily.

the blood lipids to the initially low levels. The fluctuations were most marked for cholesterol, an example of which taken from one experiment is shown in Chart 1. These findings are quite comparable with the changes in the blood lipid levels of the depancreatized dog which are produced by the ingestion of raw pancreas (Chaikoff and Kaplan¹⁴).

These initially effective results suggested that the feeding of pancreatic juice over longer periods of time might have a continuing beneficial effect on the blood lipids and a protective action on the liver lipids. Such was found to be the case. Examples of the protective action on the blood lipids are shown in Table IV. The effects of pancreatic juice feeding on liver lipids and the description of the procedures used in both the blood and liver lipid studies are presented in Section III.

(III) The Effect of the Feeding of Unactivated Pancreatic Juice upon the Liver Lipids of the Completely Depancreatized Dog Maintained with Insulin

Procedure—Five depancreatized dogs were maintained on the basic diet and eight units of insulin, twice daily, as described in Section II. In addition, 125 Gm. of raw pancreas were administered with each meal, by forced feeding when necessary, until a vigorous appetite was reestablished. The raw pancreas was then displaced by unactivated pancreatic juice (Elman-McCaughan fistula) which was fed over a period of 20 weeks. The circumstances required that the juice should be collected in San Francisco and fed in Berkeley. As a result the juice was not strictly fresh. Dogs D228, D229, D230 and D234 received an average of 377 cc. of pancreatic juice each 24 hours in amounts of about 100 to 300 cc. per meal. The mean age of the juice was 16 and 28 hours at the evening and morning feedings respectively. Dog D256 received an average of 420 cc. per day of a juice which had a mean age of five to seven hours at the time of feeding. At the end of the study, the animals were sacrificed by the intraperitoneal administration of nembutal. The livers were removed and examined as described by Kaplan and Chaikoff.¹³

Results—All of the animals were in good spirits and their nutritional condition appeared to be satisfactory although one had lost considerable weight (Dog D234 liver fatty acids 3.11 per cent). The livers showed a fatty acid content that ranged from 3.11 and 7.0 per cent as compared with the fatty acid levels of 14.4 to 29.2 per cent (average 24 per cent) that were found in the livers of 30 controls, depancreatized dogs that were observed in the laboratory for periods of 19.5 to 21 weeks on diets containing no raw pancreas. It is possible the results would have been more favorable if the juice had been fresher, and available in larger amounts (Table V).

(IV) The Effect of the Feeding of Unactivated Pancreatic Juice upon the Blood and Liver Lipids of the Dog Subjected to Successful Ligation of the Pancreatic Ducts

These studies were undertaken as controls on the observations on the depancreatized dog, maintained with insulin, since it had previously been

demonstrated that duct-ligated dogs develop fatty livers and low blood lipid levels in the absence of adequate replacement therapy. Four dogs received an average of 420 cc of pancreatic juice per 24 hours. Four other dogs were used as untreated controls. The pancreatic juice, when fed, was approximately five to seven hours old. It was obtained from animals prepared and maintained by the methods described in Section III. The juice-fed and control animals were maintained on a lean meat diet plus vitamin and salt supplements and eight units of insulin twice daily. The latter was employed to protect against a possible insulin insufficiency.

Results—Pancreatic juice was found to exert a protective action on both the blood and liver lipids which is comparable with the beneficial effects of raw pancreas^{15b, c}. The controls, with one exception, developed high fatty acid levels in the liver. The exception had a borderline fatty acid content of 7.13 per cent. All control animals showed a fall in the blood lipid levels below the preoperative figures and below the findings in the juice-fed group. The data on liver lipids are shown in Table VI. The protective action on the blood lipid levels is illustrated by data from two dogs in Table VII.

Discussion—Study of the existing data concerning the influence of ligation of the pancreatic ducts upon lipid metabolism discloses a preponderance of evidence in support of the occurrence of fatty infiltration of the liver following this procedure. The failure of Diagstedt, *et al.*,^{7a} to obtain fatty livers cannot be considered as unequivocal evidence against their appearance, outweighing that presented by other laboratories, since it may have been due to the shorter period of survival of their animals. Moreover, a "slight fatty infiltration" of the liver was noted in two of their dogs which, quite possibly, was early evidence of a change that would have become more pronounced if the animals had lived for a longer period of time. Finally, the "normal" liver, found in the third animal, which appears to carry the burden of their belief, may have been due to a short survival period or to the unexplained biologic variation which was responsible for low liver lipids in four of our 21 duct-ligated controls (Dog E23, 2.67 per cent, Dog E25, 6.32 per cent^{11b}, Dog E55, 7.60 per cent¹⁸, and Dog E59, 7.13 per cent^{17b}). It would seem, then, that one support for the lipid hormone theory is unfounded.

The existence of the second support, namely that pancreatic juice when fed, does not prevent the development of a fatty liver in the depancreatized dog maintained with insulin, must now be considered to be extremely doubtful in view of the work of Montgomery, *et al.*,^{15a, b, c} which is summarized in Sections III and IV of this paper, and in which it was shown that the administration of 377 to 420 cc of pancreatic juice per dog per day for 20 weeks kept five depancreatized and four duct-ligated dogs in good nutritional state and prevented the deposition of excessive amounts of fatty acids in their livers. This evidence is most significant because it is positive, since the material fed possessed qualities of effective control in conditions which quite uniformly lead to fatty liver formation in the absence of proper replacement therapy.

The failure of Dragstedt, *et al*,^{7a} to obtain similar results seems, therefore, to have been due to some defect in their methods or materials. It may have been a weakness in the basic regimen, since their depancreatized dogs failed to survive even with insulin replacement therapy, a circumstance which is certainly contrary to our experience. Whether this is due to the apparent lack of vitamin and salt replacements in the diet, or to failure to bring the animals safely through the postpancreatectomy depression period by forced feeding and the use of raw pancreas, whenever these methods were needed is uncertain. The failure may also have been due, in part at least, to the character and perhaps to the volume of the administered pancreatic juice. Speculation on the latter point is of limited value, since no data were given concerning the average daily dose. Concerning the character of the juice, something more positive can be said. Entenman, Chaikoff, and I (unpublished) observed in the course of the work on the influence of pancreatic juice upon the blood lipid levels in the depancreatized dog maintained with insulin,^{11a} that activated pancreatic juice from the Dragstedt, Montgomery, and Ellis¹⁷ fistula gave less consistent results than the unactivated pancreatic juice obtained from the Elman and McCaughan¹⁶ fistula. It was for this reason that juice from the latter type of fistula was used by us in the successful studies on liver lipid control.

TABLE IV

EFFECT OF INGESTION OF PANCREATIC JUICE FOR LONG INTERVALS UPON WHOLE BLOOD LIPIDS OF COMPLETELY DEPANCREATIZED DOGS MAINTAINED WITH INSULIN

Dog No	Weight	Period After Pancreatectomy	Period Fed Pancreas	Period Receiving Pancreatic Juice	Cholesterol			Total Fatty Acids	Phospholipid	Total Lipid
					Total	Free	Ester			
	Kg	Wks	Wks	Wks	Mg per 100 cc	Mg per 100 cc	Mg per 100 cc	Mg per 100 cc	Mg per 100 cc	Mg per 100 cc
D228	10.5	(1)*			142	128	14	368	315	510
	10.5	(0)			153	138	15	363	313	516
	9.9	5.8	5.8		176	138	37	356	442	531
	9.6	8.0	8.0		198	148	50	452	402	650
	9.2	10.4		1.9	166	94	72	412	336	578
	9.2	12.7		4.2	182	121	61	382	382	564
	9.1	15.4		6.9	151	85	66	308	361	459
	9.5	18.4		9.9	142	85	57	410	327	552
	9.7	19.4		10.9	165	106	59	376	365	541
	9.5	23.7		14.2	157	103	54	422	399	579
	9.5	28.0		20.0	175	110	65	453	400	628
	14.2	(2.5)			143	112	31	338	372	481
	14.7	(1)			146	106	40	311	358	457
	13.6	3	3		226	128	98	530	413	756
D256	13.5	7		4	210	117	93	524	487	734
	14.5	11		8	226	108	118	480	473	706
	14.6	14		11	205	109	96	482	371	687
	14.3	16		13	235	125	110	534	492	769
	13.3	23		20	159	105	54	419	383	578

* The numbers in parentheses refer to the number of weeks before pancreatectomy.

In the light of these observations it appears to be necessary to reappraise the statement of Dragstedt,¹⁹ "it seems important to recognize that the

absence of pancreatic juice from the intestine is relatively unimportant, leading only to a partial impairment in digestion and absorption, whereas the deficiency in the internal secretions, insulin and lipocaine, is incompatible with life." Rather than being proved to be unimportant, the evidence now shows that the exclusion of pancreatic juice from the intestinal tract by duct ligation

TABLE V

LIVER LIPIDS OF DEPANCREATIZED DOGS FED UNACTIVATED PANCREATIC JUICE*

Dog No	Weight		Period Depancreatized Weeks	Pancreatic Juice		Liver	
	Initial Kg	Final Kg		Period Fed Weeks	Amount Daily Avg Cc	Wt Gm	Fatty Acid Content Per Cent
D228	10.5	9.5	28	20	377	530	3.70
D229	9.9	9.8	28	20	377	540	7.00
D230	10.1	9.0	28	20	377	570	5.79
D234	16.7	11.1	24	20	377	535	3.11
D256	13.6	13.3	23	20	420	470	3.19
Controls							
D208	12.5	12.5	20			1100	20.40
D209	15.0	7.8	20			500	15.10
D210	10.2	7.7	20			637	20.50

* Insulin maintenance eight units twice daily

is followed by blood and liver changes that are similar to, if not identical with, those produced by pancreatectomy, and that the feeding of pancreatic juice to the depancreatized dog, maintained with insulin, results in blood and liver lipid pictures which are indistinguishable from those produced in such animals by the feeding of raw pancreas.

It seems apparent, then, that the surgeon who is called upon to permanently obstruct the external secretory mechanism of the pancreas in the course of the treatment of lesions of this gland must recognize that, if the human pattern follows that of the dog, which seems likely, the procedure will lead to major disturbances of the individual's ability to control his lipid metabolism, which must be rectified by proper replacement therapy if the retention of a healthy condition by the patient is to be assured.

CONCLUSIONS

(1) Successful ligation of the ductal communications between the pancreas and the duodenum leads to atrophy of the pancreatic acinar structures and to alterations in the blood and liver lipids that are apparently comparable, in all respects, with the known blood and liver lipid changes which have been observed in the completely depancreatized dog, maintained with insulin.

(2) Unactivated pancreatic juice fed to the depancreatized dog, maintained with insulin, or to the duct-ligated dog, controls the blood and liver lipids in a manner that is indistinguishable from that which follows the administration of raw pancreas.

(3) The external secretion of the pancreas is thus established as an essential factor in the control of lipid metabolism. The manner of its action is as yet not clearly understood.

(4) The surgeon must recognize, therefore, that the exclusion of pan-

creatic juice from the intestinal tract by operation, infection or ductal obstruction may lead to serious metabolic disturbances which must be corrected by proper replacement therapy if the patient's metabolic balance is to be restored

TABLE VI
LIVER LIPIDS OF DUCT LIGATED DOGS FED UNACTIVATED PANCREATIC JUICE*

Dog No	Weight		Period Since Duct Ligation Weeks	Pancreatic Juice		Liver	
	Initial Kg	Final Kg		Period Fed Weeks	Amount Daily Avg Cc	Wt Gm	Fatty Acid Content Per Cent
E56	12.1	16.0	23	20	420	350	2.24
E63	15.0	19.7	23	20	420	290	4.90
E65	14.3	17.0	23	20	420	317	4.08
E66	13.0	18.0	24	20	420	372	2.62
Controls							
E57	10.8	10.7	23			255	31.40
E59	9.2	7.3	23			268	7.13
E54	15.3	9.2	23			550	16.60
E60	14.8	10.5	23			381	22.70

* Dogs received a prophylactic dose of eight units of insulin twice daily (see text)

TABLE VII
EFFECT OF INGESTION OF PANCREATIC JUICE ON BLOOD LIPIDS OF DUCT LIGATED DOGS

Dog No	Weight Kg	Period After Duct Ligation Wks	Period Fed Pancreas Wks	Period Fed Pancreatic Juice Wks	Cholesterol			Total Fatty Acids Mg per 100 cc	Phospho lipid Mg per 100 cc	Total Lipid Mg per 100 cc
					Total Mg per 100 cc	Free Mg per 100 cc	Ester Mg per 100 cc			
E56	12.1	(1)*			201	125	76	425	402	626
	12.1	(0)			176	108	68	470	392	646
	12.5	3	3		172	107	65	421	332	593
	13.5	6		3	185	129	56	423	432	608
	14.4	11		8	233	140	93	393	489	626
	14.7	15		12	195	109	86	470	398	665
	15.8	22		19	205	130	75	505	486	710
	16.0	23		20	220	124	96	549	460	769
	15.0	(1)			153	116	37	388	460	541
E63	15.0	(0)			160	114	46	409	417	569
	15.4	3	3		180	122	67	498	384	687
	15.0	7		4	164	127	37	466	441	630
	18.1	11		8	196	141	55	448	382	644
	19.6	22		19	207	124	83	432	474	639
	19.7	23		20	199			473	425	672

* The numbers in parentheses refer to the number of weeks before pancreatectomy

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THE RÔLE OF THE SECOND THORACIC SPINAL SEGMENT IN THE PREGANGLIONIC SYMPATHETIC INNERVATION OF THE HUMAN HAND—SURGICAL IMPLICATIONS

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OPPORTUNITIES permitting accurate observations concerning the rôle played by a single spinal segment in the sympathetic innervation of a portion of the human body are exceedingly limited. Of necessity, our knowledge of segmental sympathetic innervation has been obtained through experiments on lower animals, yet sympathectomies performed upon man often disclose discrepancies between the anatomy of the segmental sympathetic innervation as it exists in lower animals and as it pertains to the human being.

This is illustrated in a recently published difference of opinions concerning the Telford¹ and Smithwick² operations for preganglionically denervating the blood vessels of the arm. In these operations, the connections of the first thoracic ganglion with the spinal cord are purposely left intact to avoid destruction of postganglionic fibers and the production of a Horner's syndrome. Kuntz and his associates³ have demonstrated that in lower animals the first thoracic segment contributes to the sympathetic innervation of the forelimb and, therefore, contend that the Telford and Smithwick operations are anatomically inadequate. However, on the basis of clinical observations, DeTakats,⁴ Learmonth,⁵ and White⁶ support Telford's and Smithwick's conclusions to the effect that, provided they are performed properly, these operations will completely destroy the preganglionic sympathetic innervation of the blood vessels of the human arm.

To denervate the blood vessels of the hand, I prefer the preponderantly preganglionic type of operation in which, through a posterior approach, the second thoracic ganglion, the adjacent portions of the sympathetic trunk, the connections with the second intercostal nerve, and the posterior end of that nerve are resected. Through a peculiar operative error, an opportunity was presented in one of these cases to perform a controlled study on the contribution of the second thoracic spinal segment to the sympathetic innervation of the human hand.

Case Report—Clinic No. 186, 118 E. C., white, female, age 32, was admitted to the Peripheral Vascular Clinic of Cleveland City Hospital, and gave the following history. Fifteen years previously, at age 17, she noticed, for the first time, that the fingers of both hands would become white and cyanotic on exposure to cold or during an emotional upset. At age 25, eight years later, she developed a progressive atrophic arthritis which resulted in severe deformity and crippling of her hands. In addition, she began to suffer intensely from sensations of coldness and numbness in the deformed digits. These had persisted unabated during the past eight years and she desired relief.

Physical Examination—Both hands were markedly deformed the various joints being fixed in distorted positions (Fig 1) In addition, both hands were deeply cyanotic, markedly cold to the touch, and covered with perspiration Pulsation was palpable in both radial arteries There was no ulceration, but there were beginning sclerodermatous changes in the fingers A Landis test was performed, and the skin temperatures taken



FIG 1—Roentgenogram showing chronic arthritis deformans of the hands
The arthritis was associated with a severe vasospasm

from various points on both hands reached vasodilatation levels ranging between 30.5° and 32° C Both hands became pink, and the subjective sensations of coldness and numbness disappeared It was explained to the patient that while a sympathectomy would not influence the arthritic process, it would relieve the sensations of coldness and numbness She agreed to the operation with this understanding

Operation—February, 1939 Under general anesthesia, the posterior end of the right third rib was exposed and resected The posterior mediastinum was opened, and the posterior end of the second intercostal nerve, the second thoracic ganglion, the adjacent portions of the thoracic sympathetic trunk, and the rami communicantes between the ganglion and the intercostal nerve were resected *en masse* The ganglion was sent to the pathologist for microscopic examination The following day the right hand was pink, hot, and dry Sensations of coldness and numbness had completely disappeared, the left hand remained unaffected The pathologist reported that a sympathetic ganglion had been resected Two weeks later, a similar procedure was performed on the left side, the resected ganglion being sent to the pathologist for microscopic examination

The following day it was evident, from only a cursory inspection, that a complete denervation of the left hand had not been obtained While the left hand was warmer than it had been prior to the operation, it was distinctly cooler than the right hand, and the palm of the left hand was definitely sweaty At first it was feared that some structure other than the sympathetic trunk had been removed However, the pathologist disposed of this contingency by reporting microscopic identification of a sympathetic ganglion The mystery was not cleared up until some weeks later, when a routine roentgenogram of the chest revealed that a technical error had been made during the second operation The fourth rib instead of the third rib had been resected (Fig 2) This meant that the third left thoracic ganglion instead of the second had been removed, and that the second

left thoracic ganglion and its connections with the spinal cord were intact. The bilateral anatomic arrangements resulting therefrom is shown in Figure 3. It is seen that a controlled experiment had accidentally been set up in which any difference in the extent of the sympathetic denervation between the left and right hands would indicate the presence of preganglionic sympathetic fibers emerging from the spinal cord through the ventral root of the left second intercostal nerve.



FIG. 2.—Roentgenogram of the upper thoracic region. Note that the posterior end of the third rib has been resected on the right side and the posterior end of the fourth rib on the left.

Six months later this difference was measured. At a room temperature of 25°C skin temperature readings were taken from the palms of both hands and the tips of the fingers (Table I).

TABLE I
SKIN TEMPERATURE READINGS SIX MONTHS POSTOPERATIVE

	Right	Left
Palm	31.0°C	28.0°C
1st finger	31.0°C	28.0°C
2nd finger	31.5°C	27.0°C
3rd finger	30.5°C	27.0°C
4th finger	30.0°C	27.5°C
5th finger	31.0°C	28.0°C

From Table I it is seen that the left hand was distinctly cooler than the right, the difference ranging from 2.5° to 4.5°C . (The patient volunteered the information that while complete subjective relief had been obtained in the right hand, the left hand had not been benefited to the same extent.)

A Landis test was then performed. As has been shown,⁷ a rise in the skin temperatures of the extremities in response to warming the body is dependent upon an intact sympathetic nerve supply. Forty minutes after the test had begun the temperatures were as noted in Table II.

From Table II it is seen that while the skin temperatures of the right hand were

PREGANGLIONIC SYMPATHECTOMY

TABLE II

TEMPERATURE READINGS 40 MINUTES AFTER BEGINNING OF LANDIS TEST

	Right	Left
Palm	31.2° C	32.7° C
1st finger	30.9° C	32.8° C
2nd finger	31.1° C	32.6° C
3rd finger	30.3° C	32.2° C
4th finger	30.1° C	33.0° C
5th finger	30.9° C	32.3° C

not affected by warming the body, those of the left hand rose from 47° to 56° C (Chart 1). The left hand also perspired during the test while the right hand remained dry.

Sympathectomists differ as to the precise rôle played by the second thoracic spinal segment in the sympathetic innervation of the upper extremity. Gask and Ross⁸ state that the connector cells for the preganglionic sympathetic innervation of the arm extend from the fourth spinal segment to the ninth. Livingstone⁹ reports that he has obtained complete sympathetic denervation of the upper extremity by resecting only the third thoracic ganglion. White¹⁰ gives the fourth to the eighth spinal segments as certain, with the second and third questionable. Incomplete denervations obtained with the Telford operation, as reported by Simmons and Sheehan¹¹, have been interpreted by these investigators as being evidence for the existence of preganglionic fibers from the second thoracic segment. Smithwick¹² believes that instances of regeneration following his operation also constitute strong circumstantial evidence for the presence of preganglionic connector cells in the second thoracic spinal segment. In fact, he has modified his operation to include intrathecal division of the roots of the second intercostal nerve to prevent regeneration of preganglionic neurons from this spinal segment. The reported case shows that the second thoracic spinal segment definitely plays an important part in the preganglionic sympathetic innervation of the hand.

The practical implications of these observations are that any operation designed to preganglionically denervate the blood vessels of an arm must completely destroy all white rami from the second thoracic spinal segment. In every instance, as determined by skin temperature and sweat distribution studies, complete, immediate denervation of the blood vessels and sweat glands of the upper extremity and the cutaneous vessels and sweat glands

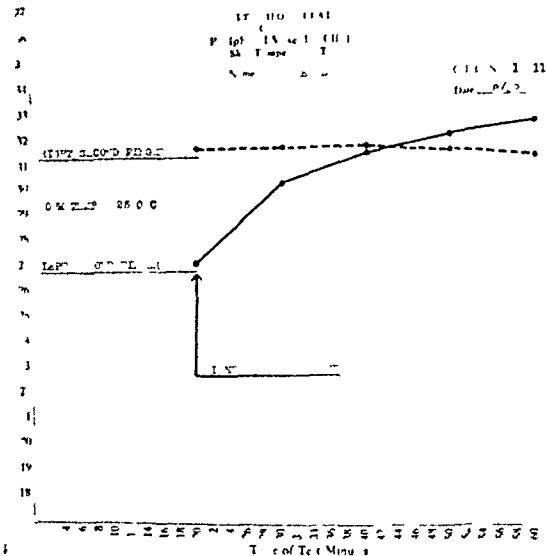


CHART 1—The chart shows response of skin temperatures of the completely denervated right second finger and the incompletely denervated left second finger to warming the body (Landis test).

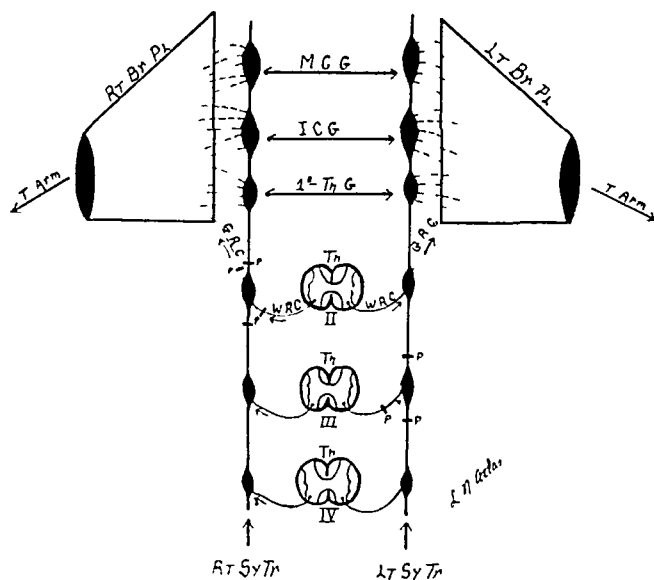


FIG 3—A diagrammatic representation of sympathetic innervation of the blood vessels of the hands after resection of the right second and the left third thoracic ganglia and their corresponding rami communicantes

Rt—Right Lt—Left Br PL—Brachial plexus, Th G—Thoracic ganglia WRC—Preganglionic rami, Sy Tr—Sympathetic ganglionated trunk, MCG—Middle cervical ganglia, ICG—Inferior cervical ganglia GRC—Postganglionic rami, P—Points of surgical division Arrows indicate direction of flow of vasomotor and sudomotor impulses



FIG 4—Photograph taken shortly after the excision of the right second thoracic ganglion for causalgia of the right hand. Patient received an intravenous infusion. Note the profuse perspiration covering the left side of the face with complete absence of perspiration on the right side of the face. Perspiration stopped exactly at the midline of face

of the corresponding half of the face should be obtained (Fig 4)

In none should a Horner's syndrome ensue

If any adrenalin sensitization has resulted from the destruction of the postganglionic ramus from the second thoracic ganglion to the brachial plexus, it has not been clinically significant in these instances in which the second thoracic ganglion has been resected. It is felt that the Smithwick and Telford operations have both been made needlessly complicated

in order to preserve this postganglionic ramus and thereby to achieve a "pure" preganglionic denervation. It appears that this desire to avoid destruction of Kuntz's nerve has also rendered these operations, except when meticulously performed, somewhat uncertain as to the completeness and permanency of the denervation which they effect. I believe that, by and large, excision of the second thoracic ganglion will prove to be essential if disappointing results are to be consistently avoided.

Another conclusion concerns the necessity of resecting the proper rib in a posterior approach to the thoracic sympathetic trunk. The usual procedure, after exposing the thoracic cage by dividing the overlying integument and muscular layers, is to palpate the

first rib and count down. However, the angle between the first rib and the corresponding transverse process is quite sharp (Fig 2). Unless care is taken to properly identify the first rib by hooking the tip of the exploring finger around its upper edge, it may be missed, in which event the second rib will be mistakenly identified as the first. Lately, it has been my practice to expose the second thoracic ganglion and its connections by resecting the second rib rather than the third. The exposure thus effected is much more adequate for the necessary manipulations.

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JEJUNOSTOMY FOR POSTOPERATIVE FEEDING*

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WE PROPOSE TO DISCUSS the use of jejunostomy with jejunal feeding in upper abdominal surgery, the value of which, we believe, is perhaps not sufficiently appreciated. We feel that this procedure has a definite place in the postoperative management of certain operations and that in some cases it is a life-saving procedure, since it permits the immediate giving of food and fluid to seriously depleted patients.

Jejunostomy has been advocated and has been used for numerous conditions and complications. Some of the indications for jejunostomy which have been advocated^{44 39 19 4 13 5 3 et al} are: To nourish a devitalized patient, to feed inoperable cases of cancer of mouth, necks, *etc.*, as a preference to gastrostomy, in extensive duodenal ulcers, in gastrojejunal ulcer, when the patient is too ill to withstand a more extensive operation, in chronic biliary, gastric and duodenal fistulae, for the nausea and vomiting of pregnancy, for pernicious vomiting and inability of stomach to empty itself after operations upon the stomach, in primary resections of small and large bowel, for intestinal obstruction, and in localized and generalized peritonitis. Obviously, jejunostomy was employed in these conditions for but one or two purposes—for feeding to improve the nutrition of a patient either before or after an operation, or to place portions of the gastro-intestinal tract at rest.

In 1885, Gould and Lee¹¹ reported one of the earliest jejunostomies performed for feeding purposes. Golding-Bird¹⁰ reported a similar procedure in the same year. These patients both died.

Kirschner,²⁰ in 1929, was the first to make a vigorous plea for jejunostomy in gastric resection cases in order that the patient might be kept in the proper nutritional balance and in order to prevent the 'postoperative atony of the stomach' which not infrequently follows gastric resection. He stressed the fact that many gastric resections are performed upon elderly or devitalized patients who do not tolerate further starvation postoperatively. In 1929, he had employed the procedure in 60 cases with good results. Wolfer⁴⁴ has given a very good review of the whole subject of jejunostomy with jejunal alimentation.

The Importance of Adequate Nutrition in the Treatment of Surgical Patients—Malnutrition in the surgical patient is more widespread than is commonly believed, and we are coming to recognize that even those patients

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who appear to be normal may be nutritionally depleted. Minot¹⁰ observes that "The major problems of nutrition do not concern clean-cut deficiency diseases, but the prevention of partial deficiency. Border-line states of nutritional instability are much more common than is usually appreciated. There is a wide zone between optimal nutrition and the level at which classic symptoms of recognized deficiency states develop." Since a variety of complications following operations on the gastro-intestinal and biliary tracts have been shown to be the result of prolonged nutritional disturbances, the nutrition of the patient has become of prime importance to the surgeon.

Jones and Eaton¹⁶ were the first to call attention to the hazards of hypoproteinemia in patients subjected to operations. Jones and his colleagues^{16, 17} had their observations corroborated and extended by Ravdin and his co-workers^{28, 38, 36, 33} who have stressed the importance of hypoproteinemia and nutritional edema in operations upon the gastro-intestinal tract.

There are several causes for latent or manifest edema in surgical patients. They are: Nitrogen starvation, general malnutrition, purulent and serious drainage, hemorrhage, severe diarrhea, administration of large amounts of sodium salts, increased metabolic demands associated with fever and sepsis, and retention of base due to temporary disturbance of renal function. In the past there has been much emphasis on the salt and water requirements of the surgical patient and very little thought of the protein requirements. It has long been known that the plasma proteins play an important rôle in keeping fluids in the blood vessels, but only recently has it been realized that the proper control of fluids and electrolyte balance in a patient must take into consideration the plasma protein concentration. It is known that excessive amounts of sodium chloride will produce a subcutaneous edema, particularly in the presence of hypoproteinemia, and, therefore, parenteral fluids must be used judiciously. However, it is the consensus of opinion of various investigators that low plasma proteins account for the major part of the edema. It is likewise believed that the low plasma protein is due mainly to an inadequate intake of protein before and after operation.

What are the methods available to combat an hypoproteinemia and the consequent edema? Transfusions of whole blood or serum are very helpful in restoring plasma protein in an hypoproteinemia patient but these are only temporary aids because the basic problem is one of protein regeneration. Intravenous administration of amino-acid products and lyophilized serum are, admittedly, not yet efficacious in restoring plasma proteins.³³ A restriction of the intake of sodium chloride is important in preventing edema, particularly in patients with lowered plasma proteins. A high protein intake, however, is the one method we have for a permanent restoration of plasma proteins. We believe, with others^{16, 3} that low plasma proteins in surgical patients are due, in most part, to a reduction in the intake of protein *before and after* operation. Since the alimentary tract is still the best route to supply the necessary elements for protein regeneration, and thereby cause a permanent increase in the plasma proteins we feel that jejunal alimentation is the best

method to employ when the nature of the disease, or the operation, prevents any intake by mouth, for several days

During the past few years, it has become increasingly obvious that the vitamins play a very important and necessary rôle in the proper nutrition and well-being of an individual. There is ample evidence now that many people live in a chronic state of vitamin deficiency, due to an insufficient or unbalanced diet. A considerable number of patients with gastro-intestinal lesions have for some time prior to admission to the hospital received an inadequate nutrition, more particularly when anorexia, vomiting and pain are present, and some of them have a subclinical or clinical deficiency of certain of the vitamins. Fortunately, the effects of a vitamin deficiency can be corrected quite promptly.

Vitamin A provides for a healthy epithelial structure and, therefore, is one factor in the prevention of postoperative bronchitis, pneumonia and urinary tract infections. The vitamin B complex is important for the proper function of the gastro-intestinal tract. Ravdin *et al*³³ have demonstrated that a vitamin B deficiency prolongs the emptying time of the stomach. The lack of intercellular cement in vitamin C deficiency is one of the causative factors in wound disruption^{22 37} and subcutaneous edema. One need only note the edema, hemorrhages and poor healing of a patient with scurvy to find proof for this statement. The use of vitamin K in raising the prothrombin level of the blood is now well-established.

There is theoretical, experimental and clinical evidence that a sufficient protein and vitamin intake will lessen the chance of postoperative infections, will lessen the amount of edema in the operative area, will give a better and firmer healing of wounds, will permit a more normal function of the gastro-intestinal tract, and smoother postoperative convalescence. Therefore, we feel that it is most important to immediately correct these nutritive deficiencies preoperatively if the patient is able to take food by mouth and to continue a diet rich in proteins and vitamins postoperatively by means of jejunal alimentation.

Types of Food for Jejunal Alimentation—The pabulum suggested by Scott, Ivy and Holinger^{34 35} is undoubtedly a good one when prolonged or permanent jejunal alimentation is to be carried out. However, we have found that a simple formula is entirely satisfactory for complementary feedings during the postoperative period after upper abdominal surgical procedures. We have used the following formula with consistently good results—500 cc milk (peptonized*), one egg, 6 mg thiamin chloride, 15 cc vitamin B complex syrup, 300 mg cevitanic acid, and three drops of Haliver oil with Vio-sterol. This amount of the formula yields approximately 380 calories. In the last few cases, we have used skimmed milk, thereby eliminating practically all of the fat from the pabulum, and there have been no cases experiencing diarrhea, as did a few when whole milk was used. The milk and well-beaten eggs are peptonized and then the vitamin concentrates are added. It may be administered by a simple "drip" apparatus.

* Peptone from Fairchild Bros & Foster, New York, N Y

The jejunal feedings are started 12 to 24 hours after the patient has been returned from the operating room. Only 200-300 cc of the pabulum is taken from the refrigerator and placed into the flask of the drip apparatus at one time. At first, the pabulum is allowed to drip so that about 50 cc is introduced into the jejunum each hour, in order that the jejunum may become accustomed to the feedings. The pabulum is too thick to "drip" like parenteral fluid and it requires the attention of a nurse occasionally to see that it is running in at the proper speed. Gradually, during the next 24-48 hours, the amount of pabulum allowed to run in is increased to 100 cc per hour, and this is continued day and night. Naturally, the amount of pabulum and the rapidity with which it can be introduced will vary with the individual tolerance for the jejunal feedings. No set rule can be used for all cases. We try to introduce 2,000-3,000 cc of pabulum over the 24-hour period after the second or third postoperative day. Unless the pabulum is introduced slowly the patient will have abdominal distress and he may experience nausea, vomiting or diarrhea, the latter may be controlled by the addition of small doses of paregoric to the feeding.

For the first two or three days after operation, aspiration of the stomach is carried out at 12-hour intervals. If there is any significant amount of upper gastro-intestinal secretions obtained by aspiration, these important juices are placed in the jejunal feedings, so that the patient will have the use of these vital elements which would otherwise be denied him. Vitamin K concentrates and iron products are added to the feedings when these are indicated. Also, we have used the pabulum as a means of giving codeine, aspirin and the barbiturates for analgesia and sedation, and we believe the patients experienced a more comfortable postoperative course with this method of sedation. The lack of thirst and hunger with this method of feeding added to the smoothness of the patients' convalescence. In all cases, we wait until at least the twelfth postoperative day, so that a definite fistula will have been established before we remove the tube.

Indications—Jejunostomy, as a complementary procedure, should be considered in the following situations

I GASTRIC OPERATIONS

- (1) Total gastrectomy
- (2) Subtotal gastrectomy
- (3) Posterior gastro-enterostomy
- (4) Gastroduodenostomy
- (5) Resection of gastrojejunal fistula

Anyone who has had much experience with gastric surgery has had cases in which the stomach would not empty itself properly following operation. This has been called the "vicious cycle of vomiting," "postoperative atony of the stomach," and "postoperative gastric retention." A poorly functioning gastro-enteric anastomosis renders convalescence longer and unpleasant, because of vomiting and possibly produces a critical state.

The recognized causes of edema in and around a gastro-enteric stoma are

(a) *Inflammatory*—This is more pronounced in the carcinomatous gastric ulcer, where there is apt to be little or no free HCl present, and there is likely to be some infection, with its consequent edema at the site of the anastomotic stoma

(b) *Low Plasma Protein*—Due to an inadequate intake of protein pre-operatively, on account of digestive symptoms occasioned by the disease, patients undergoing gastric operations are prone to have low plasma proteins. The low plasma protein is lowered further by the pre- and postoperative administration of parenteral fluids and by the enforced postoperative period of protein starvation on account of the nature of the operative procedure. Ravdin *et al*²⁸⁻³³ have demonstrated a delay in the gastric emptying time in hypoproteinemic patients and animals before and after operations upon the stomach

(c) *Low Vitamin C Level in Body*—When there is inadequate vitamin C, there is loss of intercellular cement in the walls of the small blood vessels, which allows the plasma proteins to escape from the vessels in an abnormal amount, and thereby causes edema of the tissues

(d) *Too Much Sodium Chloride*—One can observe edema of the subcutaneous tissues when an excessive amount of saline has been administered, and this evident edema is an external sign of a generalized process taking place throughout the body

(e) *Operative Trauma*—Trauma, as a result of the operative procedure is a recognized cause of local edema in any area of the body

It appears that continuous jejunal feedings of high protein and vitamin content will reduce the edema of the operative area to a minimum

Abbott and Rawson¹ have devised a double-lumen tube which is passed through the stomach and into the jejunum *via* the gastrojejunostomy stoma at the time of operation. By this tube, food can be introduced into the jejunum and, at the same time the stomach can be kept empty by suction through the other lumen of the tube. Ravdin¹⁻⁶ is an advocate for this type of tube for feeding patients following gastric operations by what he calls the "oro-jejunal" method. We have employed this tube on one occasion without any untoward results, but we are cognizant of some disadvantages connected with its use. It is rather uncomfortable to the patient after two or three days, and he is apt to have considerable discomfort in the nose and pharynx from irritation. Also, should the patient vomit and dislodge the distal end of the tube, or should he pull it out, it cannot be reinserted. We, at present, prefer jejunostomy to the Abbott-Rawson tube for postoperative feeding of extensive stomach operations

II SURGERY OF THE BILIARY TRACT

- (1) Cholecystogastrostomy
- (2) Hepaticoduodenostomy
- (3) Repair of common duct strictures

Lesions requiring the foregoing operations are apt to be associated with debilitation from an inadequate food intake, from jaundice, and from loss of bile. Jejunal alimentation, postoperatively, puts the stomach and duodenum at rest and thereby creates an environment more conducive to firm healing of the operative procedures.

III. ANY EXTENSIVE UPPER ABDOMINAL OPERATION

In any operation in the upper abdominal area after which the patient will not be able to take food by mouth for several days, jejunal alimentation offers an ideal way of maintaining the proper nutritive status of the patient. This is particularly important if the patient is debilitated on account of his lesion and on account of an inadequate food intake prior to the operation, as in a gastro-jejunocolic fistula.

Table I gives a list of 14 recent consecutive cases in which we have employed jejunostomy for postoperative feeding purposes, because we felt that these patients had been on an inadequate diet for some time prior to their operation, or that their operative procedures warranted postoperative jejunal feeding in order that their recovery would be smoother and shorter. There was no mortality in these cases.

TABLE I
FOURTEEN OPERATIONS PLUS COMPLEMENTARY JEJUNOSTOMY

Diagnosis	Operation	Days in Hospital After Operation
1. Carcinoma of stomach	Total gastrectomy	16
2. Carcinoma of stomach	Total gastrectomy	19
3. Chronic duodenal ulcer	Subtotal gastrectomy	16
4. Carcinoma of stomach	Subtotal gastrectomy	20
5. Stricture of common duct	Hepaticoduodenostomy	17
6. Gastric ulcer	Subtotal gastrectomy	17
7. Chronic duodenal ulcer with pyloric obstruction	Gastroduodenostomy	19
8. Carcinoma of pancreas	Cholecystogastrostomy	14
9. Carcinoma of jejunum	Posterior gastro enterostomy	18
10. Gastric ulcer	Subtotal gastrectomy (Had postoperative lung abscess and osteomyelitis of sacrum)	59
11. Carcinoma and polyposis of stomach, angina pectoris	Subtotal gastrectomy	20
12. Gastrojejunocolic fistula	Resection of gastrojejunocolic fistula	15
13. Chronic duodenal ulcer with pyloric obstruction of three weeks' duration	Posterior gastro enterostomy	20
14. Chronic duodenal ulcer	Subtotal gastrectomy	25

Technic of Jejunostomy—We have employed the simplest technic⁴ in performing jejunostomy. The four illustrations (Figs. 1, 2, 3 and 4) with their legends make this sufficiently clear so that further description in this text seems unnecessary.

This method of performing jejunostomy is a combination of steps selected from various more complicated procedures advocated by others. It is an adaptation of the Stamm gastrostomy, which Hofmeister,¹⁴ in 1905, recommended for use on the intestines. Long,²⁴ Mayo,²⁶ Clue,⁴ and others, have written about, and have advocated this type of enterostomy.

This technic has given us very gratifying results. It is very simple, with small chance for a technical error. It requires only two to four minutes to perform, and, therefore, does not add materially to the time or to the scope of the primary operation. The omentum prevents any leakage around the catheter.

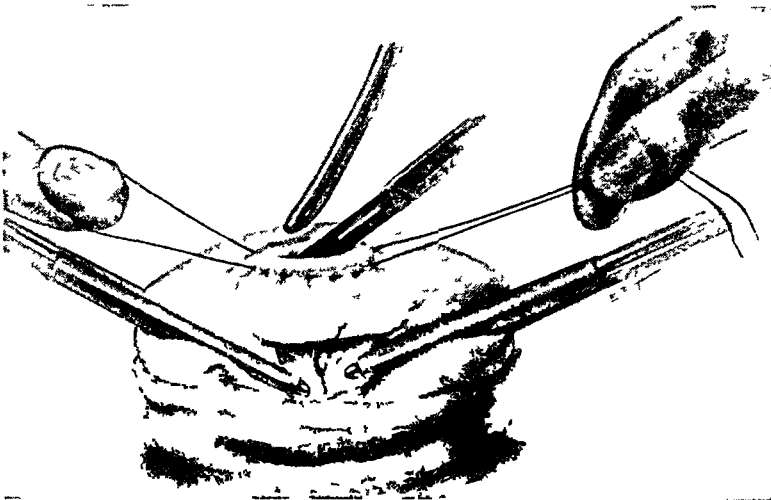


FIG 1—A loop of jejunum 20 or 30 cm away from the ligament of Treitz is isolated with intestinal clamps. A double-eyed catheter is led through adjacent omentum. A purse string suture is placed in the intestine and a stab opening made inside it. The catheter is placed in the bowel pointing distally, and the purse string tied about it.

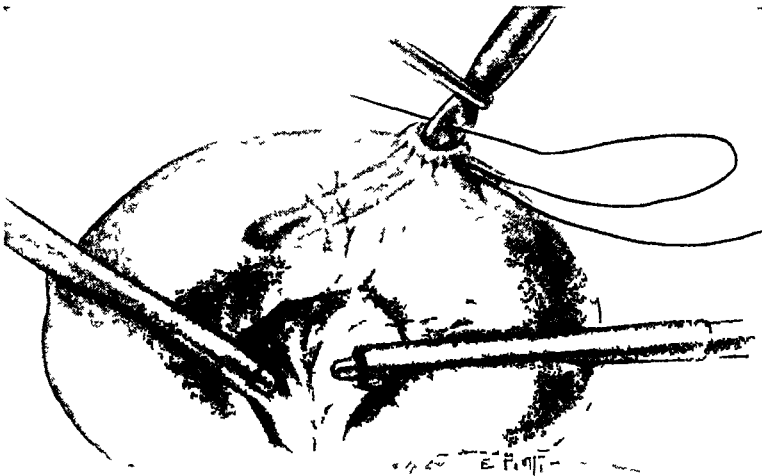


FIG 2—After the knot is tied in the first purse string suture the same thread is carried through the catheter to hold it in its position.

into the peritoneal cavity, and we have had no trouble with intestinal contents escaping to the surface of the abdominal wall and causing digestion of the skin. Perforation of the bowel by the tip of the catheter,²¹ and the fear that the second purse-string might encroach upon the lumen of the bowel are complications which we have not encountered.

It has been said that the fistula may not close spontaneously when this technic is used. In 60 cases of enterostomy performed by this technic for

POSTOPERATIVE JEJUNAL FEEDING

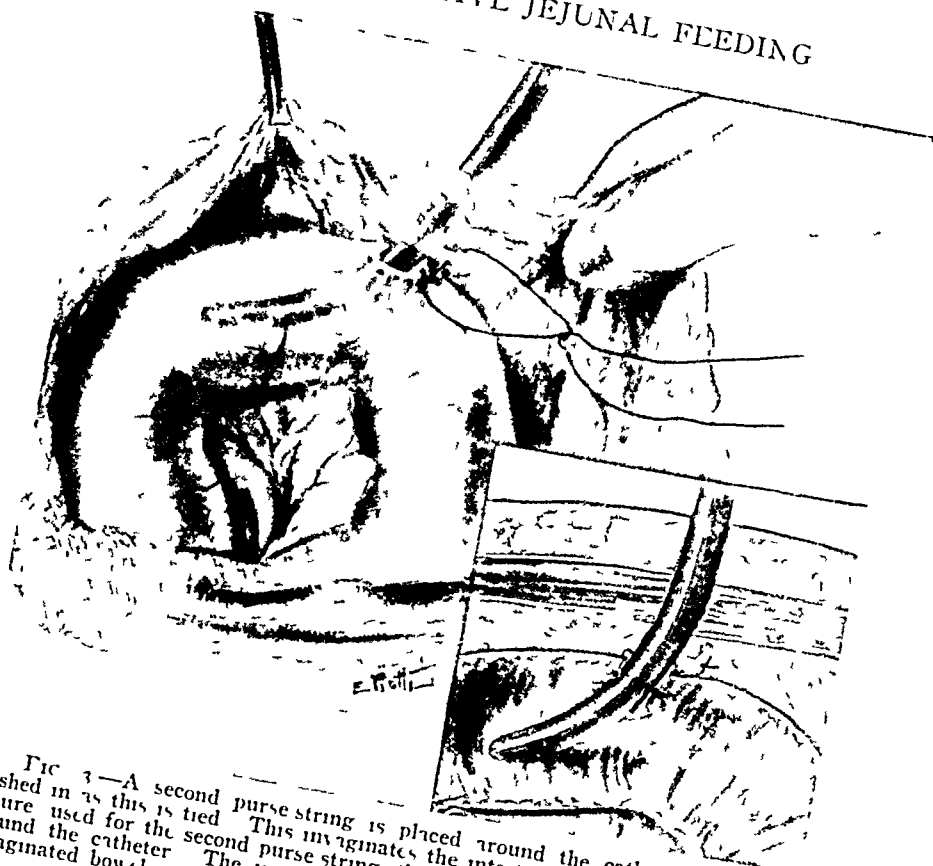


FIG 3—A second purse string is placed around the catheter which is pushed in as this is tied. This invaginates the intestinal wall. With the same suture used for the second purse string the omentum is caught and tied down around the catheter. The insert shows, in cross section, the relations of the invaginated bowel wall to the catheter, the omentum, and the abdominal wall.

various reasons during the past five years there has never been a case in which the fistula did not close spontaneously. In cases in which jejunostomy was

established for feeding purposes, there has been only a very slight amount of drainage for 18-36 hours after the catheter is removed. In a recent case in which jejunostomy was performed as a secondary operation for feeding purposes after a gastric resection, the catheter remained in the jejunum for 30 days. Following the removal of the catheter, there was no more than 15-20 cc of drainage and the fistula closed without further drainage after 36 hours. We have encountered no cases of wound infection in these feeding cases, such as may happen when an enterostomy is performed for drainage purposes in instances of intestinal obstruction or peritonitis. One must be certain that enough time (at least 12 days) has elapsed to have a definite fistula established before removing the catheter.



FIG 4—When no omentum is available for interposition between the bowel and the parietal peritoneum the second purse string suture is passed into the parietal peritoneum at the angle of the wound. This seals off the point of enterostomy.

CONCLUSIONS

(1) Malnutrition in surgical patients is widespread and of varying severity. Postoperative care, to-day, in surgical cases must continue the preoperative treatment of nutritional deficiency.

(2) Inadequate fluids, hypoproteinemia and vitamin deficiencies are especially common in surgical lesions of the upper gastro-intestinal tract. These can best be managed by supplying proper food through the gastro-intestinal tract.

(3) A simple jejunostomy at the time of operation provides a safe means for immediate administration of food and fluid, after operation, through the proper body channels.

(4) A description of the technic of the enterostomy and a list of recent cases for which it was employed, is given.

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STUDIES ON THE USE OF METALS IN SURGERY

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PART I

COMPARATIVE DETERMINATIONS OF THE CYTOTOXICITY OF CERTAIN METALS IN FIBROBLAST CULTURE*

AN IDEAL METAL for use in bone surgery should be noncytotoxic, light, and so strong that the bulk of the appliance could be kept small. Its value would be still further enhanced if the physical properties were such that it not only cast well but existed in a malleable form, particularly if, in the latter state, it could be quickly hardened by heating.

A number of noncytotoxic metals and alloys are in existence, several of which are quite satisfactory for internal splinting of bone. Of these, stainless steel and Vitallium are perhaps two of the best examples. The latter has been carefully studied in both animals and man by Venable and his coworkers,^{1, 2} who have convincingly demonstrated its usefulness. Our observations upon the effect of Vitallium upon the rate of growth of fibroblasts in tissue culture (see below), and, thus far, of its tolerance (in the form of plates) *in vivo*, afford further corroboration of its applicability in bone surgery.

If, at operation, the available appliance cannot be fitted satisfactorily, it would be very convenient to be able to alter its shape as desired, then quickly to harden it. This, so far as we have been able to learn, cannot be carried out with Vitallium, for it is not malleable.

While searching for a metal which would conform to the above-mentioned requirements, and which would be suitable for the repair of extensive cranial defects, our attention was called to a relatively new alloy, Ticonium. It is made up of nickel, cobalt, chromium, and molybdenum, with a small amount of beryllium added if it is to be cast. The physical properties† are quite

* A study of the use of various metals for the repair of cranial defects was undertaken at the same time, which will be published shortly.

† The metallurgic properties‡ of this alloy in its two different forms are

(1) *Casting Alloy*—This alloy, which is used in casting, has the following composition: Nickel 35.6 per cent, cobalt 29.1 per cent, chromium 27.7 per cent, molybdenum 6.0 per cent, beryllium 1.6 per cent. This metal has the lowest melting point of any alloy in the so-called chromium alloy series and, due to the presence of beryllium, can be cast to a high degree of fidelity. Its physical properties are as follows:

satisfactory—it is strong, rather light, and can be very accurately cast or wrought

We have been studying the tolerance of Ticomum, by living tissues, and hence its applicability in surgery both *in vitro* and *in vivo*. The present communication is an account of our observations of the effect of Ticomum, Vitallium, and other metals upon the growth of fibroblasts in tissue cultures. A subsequent report will record our studies of local tissue response to plates and screws in the dog's skull. The evidence thus far obtained, indicates that Ticomum, like Vitallium, silver gold, and stainless steel, is not cytotoxic.

Method—Ménégaux, Odiette, and coworkers^{3 4 5 6 7 8} have conclusively shown that the cytotoxicity of metals can best be studied in tissue cultures. Lately, the method of these authors has also been used by G. Krull,⁹ and by A. H. Smook and Gaillard.¹⁰

The determination of the cytotoxicity of the metals, as carried out in the present study, is based upon the rate of growth of pure fibroblast cultures (obtained from the heart of a chicken embryo) in the presence of different metals. All these observations have been made on different generations of one and the same fibroblast strain. This strain was started February 21, 1940, and was discontinued June 21, 1940, in its forty-first generation. In order to assure growth of pure fibroblasts for actual determinations, we did not use any generations previous to the tenth generation.

Metal disks[§] were prepared similar to those described by Ménégaux, Odiette, and Moyse.¹ Each disk measured 1.5 Mm. in diameter, and 0.25

Rockwell hardness C 30, yield point 65,000–68,000 lbs. per sq. in., ultimate strength 90,000–93,000 lbs. per sq. in., elongation 6 per cent. The alloy may be heat treated if desirable to be hardened or softened. During the hardening treatment, the alloy is heated to 2,000° F., quenched, and then drawn to 1,300° F. The alloy then increases in hardness to Rockwell C 40–45 and the yield point also raises to 85,000–95,000 lbs. per sq. in. This alloy in the hardened condition is quite brittle. During the softening treatment, the alloy is drawn to 2,000° F. The alloy then softens to Rockwell C 18 and the yield point drops to about 45,000 lbs. per sq. in. In the softened condition, the alloy can easily be worked or machined if desired.

(2) *Wrought Alloy*—The alloy which is used in wrought stock has the following composition: Nickel 36.2 per cent, cobalt 29.6 per cent, chromium 28.2 per cent, molybdenum 6.0 per cent. Its properties depend upon the amount of cold work done after the last anneal. For example, stock drawn to 50–60 per cent cold reduction in area after final anneal: Ultimate strength 237,000 lbs. per sq. in., yield point 177,000 lbs. per sq. in., elongation 6 per cent. Stock drawn to a 30 per cent cold reduction in area after final anneal: Ultimate strength 220,000 lbs. per sq. in., yield point 183,000 lbs. per sq. in., elongation 6 per cent. Stock drawn and fully annealed: Ultimate strength 150,000 lbs. per sq. in., yield point 96,000 lbs. per sq. in., elongation 31 inches on ten inches gauge length (52 per cent on two inches gauge length), hardness Rockwell B 95.

‡ The metallurgic data were made available by Mr. E. Touceda from the Touceda Laboratories, Albany, N. Y.

§ The metal disks were kindly prepared by the Touceda Laboratories in Albany, N. Y., and the Vitallium by the Austenal Laboratories in New York City.

Mm in thickness. We have carried out our determinations on eight different metals, namely, gold, silver, Ticonium (casting alloy), Ticonium (wrought alloy), Vitalium stainless steel, vanadium and copper.

Throughout the various experiments we have compared the different metals with each other as well as with control cultures containing no metal. As an additional control, we have used cultures containing gold disks, as gold has proved to be nontoxic to fibroblast cultures (Ménégaux and associates⁷).

Technic—Explants from the heart muscle of an 11-day-old chick embryo were prepared and cultivated by means of the hanging-drop technic. The medium used consisted of chicken plasma, chick embryo extract and Tyrode solution. The blood necessary for the preparation of the plasma was obtained under sterile precautions from young roosters by cardiac puncture. Heparin (1 mg per 1 cc saline) was used in order to prevent coagulation. The blood was then centrifuged for ten minutes at 2300 R P M. After centrifuging, the supernatant plasma was withdrawn with pipettes. Small amounts of plasma were placed in previously autoclaved test tubes and stored in the refrigerator. Fresh plasma was prepared every two to three weeks.

For the preparation of embryonic tissue extract, eggs were incubated for eight or nine days at a temperature of 38.5° C. Twenty-four hours before the transplantation, the embryo was removed to a sterile watch-glass and reduced to a pulp by the use of a fine scissors. The undiluted pulp was then stored in the refrigerator. Immediately before the transplantation, the extract was centrifuged for ten minutes at 2300 R P M. The supernatant fluid was withdrawn and mixed with Tyrode solution (3:0 dilution).

The Tyrode solution was prepared as described by Parker¹¹. The pH of the solution was kept at 7.4-7.6. We have found that it is of the utmost importance to keep the pH at this level, for the rate of growth, as well as the type of growth, was influenced immediately whenever the pH was changed. The pH was checked colorimetrically at frequent intervals. The completed mixture was passed through a Seitz filter and was then stored in small amounts in the refrigerator in rubber-stoppered test tubes. For transplantation, each culture was divided into two or four approximately equal parts, and each part placed in a drop of plasma upon a new coverslip. One equal-sized drop of embryonic tissue extract, which had been mixed previously with Tyrode solution (3:1), was added and the hanging-drop culture sealed upon a round depression slide by the use of vaseline. As soon as coagulation had taken place, the cultures were placed in an incubator at a temperature of 38.5° C. Every two or three days these cultures were transferred to a new medium until finally nothing but fibroblasts were growing. With the tenth generation we started our experiments. Each transplant of this generation was divided into four equal pieces. These pieces of tissue were implanted in a hanging-drop. A Ticonium disk was added to the first transplant, a gold disk to the second, a copper disk to the third and the fourth transplant was cultivated without any metal. The disks were placed fairly close to the tissue (Figs

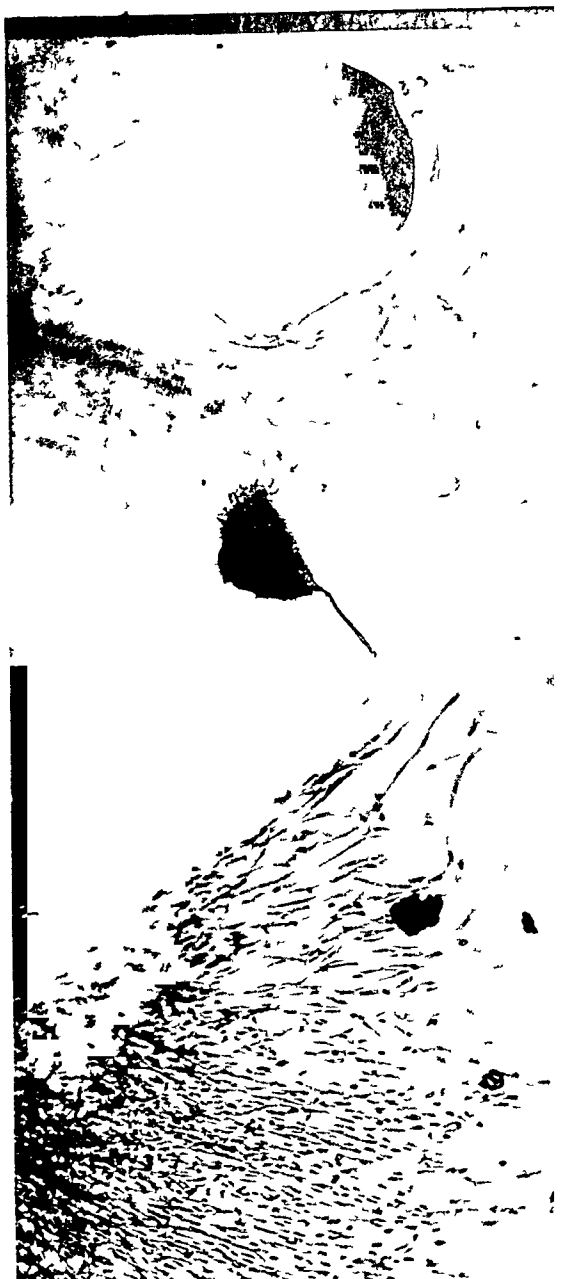


Fig. 2.—Fibroblast culture (eleventh generation) in presence of a copper disk. No growth. Note distinct difference between non-plank and copper disk (Hansen's hematoxylin stain [$\times 34$])



Fig. 1.—Fibroblast culture (thirty eighth generation) in presence of a silver disk (Hansen's hematoxylin stain [$\times 23$])



Fig. 5.—Section of fibroblast culture (eleventh generation) in presence of titanium disk (Hansen's hematoxylin stain [$\times 550$])

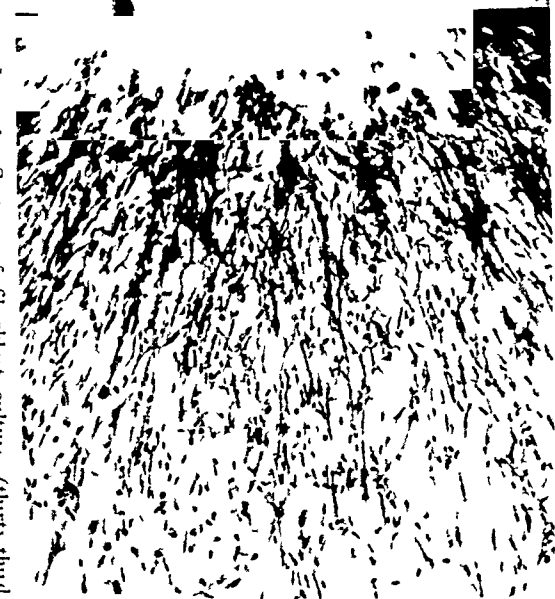


Fig. 6.—Section of fibroblast culture (thirty third generation) in presence of titanium disk (Hansen's hematoxylin stain [$\times 112$])



Fig. 4.—Section of fibroblast culture (eleventh generation) in presence of titanium disk (Hansen's hematoxylin stain [$\times 112$])

1 and 3) After coagulation had taken place, the outline of each culture was drawn by use of the camera lucida and placed in the incubator immediately afterward. After exactly 48 hours, the cultures were again drawn by use of the camera lucida at the same magnification. Subsequent experiments were carried out in a similar manner.

By use of a planimeter, the area of the original fragment as well as the total area was measured. The absolute increase of the fragment was obtained by subtracting the area of the original fragment from the total area. The absolute increase of the fragment was then divided by the area of the primitive fragment, thus determining the relative increase of the fragment (Ebeling^{1,2}). This value we have called the "factor of growth."

We realize that this method of surface measurements fails to take into consideration the growth in the third dimension, however, we have felt it to be of value to show these figures for they are a means of expressing all the significant variations which we have seen in this comparative study of cytotoxicity.

TABLE I
ELEVENTH GENERATION

Relative Increase of the Fragment in the Presence of			
Ticonium (casting alloy)	Gold	Copper	Control
11 00	11 00	0 00	14 90
8 87	4 16		12 00
5 81	9 10		7 97
14 80	7 80	0 00	13 10
	6 00	0 00	9 90
12 40	9 40	0 00	11 70
13 40	11 60		14 00
	10 70		9 00
4 20	7 40		6 30
Averaged Factor	10 07	0 00	10 98
Maximum	+4 73		+3 02
Minimum	-5 87		-4 68

TABLE II
THIRTY-THIRD GENERATION

Relative Increase of the Fragment in Presence of			
Ticonium (wrought alloy)	Vitalium	Vanadium	Control
7 8	5 1	0 00	5 3
8 2	6 6	0 00	6 8
7 4	7 0	0 00	6 8
10 1	9 1		
10 6			
15 1			
Averaged Factor	9 9	0 00	6 3
Maximum	+5 2		+0 5
Minimum	-2 5		-1 0

Experiments—In every experiment, the average factor of growth of the fibroblast cultures for each metal was calculated. Table I shows the growth factors of the fibroblast cultures in their eleventh generation, Table II, those of the cultures in their thirty-third generation.

Of the 41 generations, 13 generations were chosen for our determina-

tions A total of 222 fibroblast cultures have been examined, 31 control cultures without any metal disks have been examined and measured, gold was tested in 24 cultures, silver in 21, Ticonium (casting alloy) in 40, Ticonium (wrought alloy) in 31, Vitallium in 13, stainless steel in 23, vanadium in 21 and copper in 18 cultures

The average factor of growth of the fibroblast cultures for each metal, as obtained from the different generations, used thus for study, is summarized in Table III

TABLE III
AVERAGE OF THE RELATIVE INCREASE OF THE FRAGMENT ("FACTOR OF GROWTH")

Generation	No of Cultures	Ticonium (cast)	Ticonium (wrought)	Gold	Silver	Vitalium	Stainless Steel	Vanadium	Copper	Control
11, a	29	10 07		8 57					0 00	10 98
11, b	13	8 60		8 50						
15	14	10 80		9 40						
18	4							0 00		7 74
19	16		5 70							5 70
25	30	6 00					8 93	1 80		
26	16		6 40	0 20			6 34			
28	13		24 10				8 90	0 00	0 00	
29	15	7 50	8 90						0 00	
33	16		9 90			7 00		0 00		6 30
38	21				8 00					8 00
39	19		7 05		8 94		5 28	1 77		
41	15		23 18		13 00	16 49				
Averaged Factor		8 59	9 31	8 91	10 28	11 74	7 36	0 71	0 00	7 74
Maximum		+2 21	+14 79	+0 40	+2 72	+4 45	+1 57	+1 09		+3 24
Minimum		-2 59	- 3 61	-0 41	-1 38	-4 74	-2 08	-0 71		-2 04

A number of cultures were fixed in neutral Ringer-formol solution (Parker¹¹), and have been stained with Hansen's hematoxylin (Figs 1, 2, 3, 4, 5, 6) for purpose of illustration

Before we started the strain used for the evaluations given above, we studied the influence of different metals upon the rate of growth of about 200 fibroblast cultures, which were discarded after observation The results of these single experiments correspond with our findings obtained from the strain described above

(1 *Control Cultures* —For five different generations we prepared a total of 31 cultures, cultivated without any metal disk in the medium Table III shows the average factors of growth for the different generations The average factor of growth for all 31 cultures was calculated to be 7 74 It is well-correlated with the factors obtained for those metals that we will show to be nontoxic The difference between these control cultures and the two toxic metals (vanadium and copper) in our series is obvious

(2 *Gold and Silver* —As stated above, for five different generations, we prepared a total of 31 cultures without any metal disk In the remaining eight generations, we have used metals as controls, for instance, gold which has been proved to be noncytotoxic (Ménégaux and Odiette⁷) We thought that it would be interesting to compare the growth in the presence of these

nontoxic metals with the growth in the presence of those metals which we have been investigating for their possible use in surgery

For four generations we cultivated fibroblasts in the presence of gold disks. This represented a total of 24 cultures. The average of the relative increase of the fragment amounted to 8.91. Silver disks were implanted in 21 cultures belonging to three different generations. The average factor of growth amounted to 10.28.

(3) *Ticonium*—For five generations we prepared cultures with the "casting alloy" Ticonium, representing a total of 40 fibroblast cultures. The factor of growth averaged 8.59. The factor of growth for the "wrought alloy" Ticonium was 9.31. It was obtained from a total of 31 cultures studied in seven different generations.

(4) *Vitalium*—Thirteen cultures were used for testing the alloy vitalium. These 13 cultures were chosen from only two different generations. In the thirty-third generation the average factor of 7.00 was obtained (Table II). For the forty-first generation, the factor for Vitalium was 16.49. In the forty-first generation, however, the factor for silver was 13 while that of the "wrought alloy" Ticonium was 23.18.

The fibroblast cultures for this generation obviously grew luxuriantly, thus raising the average factor of growth above the level obtained in other experiments. That the average area of growth for Vitalium amounted to 11.74, may be explained by the fact that Vitalium was tested in this generation and in one other only, whereas the "wrought alloy" Ticonium was tested in seven different generations.

(5) *Stainless Steel*—This metal was tested in a total of 23 cultures obtained from four different generations. The average factor was 7.36.

(6) *Vanadium*—Twenty-one cultures were tested with Vanadium in five different generations. Thirteen of these cultures did not grow at all. The remaining eight showed a marked inhibition of growth, the average factor of growth was 0.71. Clinically, the failure of this metal has been reported repeatedly. We have now obtained proof *in vitro* for the high cytotoxicity of this alloy.

(7) *Copper*—Copper was tested in three different generations with a total of 18 cultures. None of these cultures showed any growth of fibroblasts.

Discussion—The evaluation given above draws a definite line between the six nontoxic metals and vanadium and copper both of which prove to be highly cytotoxic. We have based our determinations on one criterion—the actual growth of fibroblasts in the presence of metals.

Copper in its pure form may be considered completely cytotoxic since no growth was obtained in any of the cultures containing it. Vanadium may be regarded somewhat less cytotoxic than copper for a slight growth was obtained in eight of 21 cultures and no growth at all in the remaining 13. The cytotoxicity of vanadium in our cultures is of such a degree as to make the

use of this substance in bone surgery inadvisable. Its cytotoxicity is the probable explanation of the failures reported of its use in clinical surgery.

Five of these substances (gold, silver, Vitallium, and two Ticonium compounds) gave a factor of growth higher than the control cultures without metal disks. Stainless steel gave a result slightly higher than the controls without disks.

We do not feel that any conclusive deductions can be drawn from the varying rates of growth of the metals we have found to be noncytotoxic.

SUMMARY

(1) The cytotoxicity of the eight metals (gold, silver, Ticonium (casting alloy), Ticonium (wrought alloy), Vitallium, stainless steel, vanadium, and copper) was determined by measuring the area of growth of fibroblast cultures in the presence of these metals.

(2) Gold, silver, Ticonium (casting alloy), Ticonium (wrought alloy), Vitallium and stainless steel are found to be nontoxic. Vanadium and copper are found to be highly cytotoxic.

The authors wish to express their appreciation to Dr. Joseph Schwind of the Department of Anatomy, for his help and advice in this work, and to Mr. E. G. Touseda for his interest in the metallurgic phase of the study. Mr. John Ziegler also rendered valuable assistance.

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BOOK REVIEW

TREATMENT OF CANCER AND ALLIED DISEASES Edited by GEORGE T. PACK, M.D.,
Attending Surgeon, Memorial Hospital, New York, N. Y., and EDWARD M. LIVINGSTON,
M.D., Assistant Attending Surgeon, Memorial Hospital, New York, N. Y. New York
and London Paul B. Hoeber, Inc., 1940

THIS THREE VOLUME WORK, prepared by 147 international authors, and consisting of 2,595 pages and 1,500 illustrations, is an amazing accomplishment, and the publishers as well as the authors have reason to be proud of the result. The binding, the paper, the type are superfine, and the uniformity of excellence of the enormous number of illustrations, supplied by nearly 150 authors, is almost unbelievable.

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The consideration of the lesions as they involve special tissue and organs makes the subject matter readily available, and the vast experience of the authors guarantees a statistical value far above that which can be credited to many of the publications now in our surgical literature. Volume I contains 52 chapters devoted to lesions of the head, face, neck, breast and chest, while volume II, consisting of 42 chapters, is concerned with lesions of the esophagus, gastro-intestinal tract, and female genitalia. Volume III has 47 chapters, in which the lesions of the urinary system, male genitalia, skin, nervous system, bones, joints, lymphatic system, and such miscellaneous subjects as anesthesia, experimental therapy and nursing care are considered.

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WALTER ESTELL LEE, M.D.

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RESULTS OF PARTIAL GASTRECTOMY FOR BLEEDING DUODENAL, GASTRIC, AND GASTROJEJUNAL ULCER *

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Types of Bleeding Peptic Ulcer —Two principal types of gross hemorrhage occur from peptic ulcer the chronic, which is associated with hematemesis or melena but does not give rise to severe symptoms of loss of blood even though the bleeding may be considerable, and the acute massive, which is associated with marked sweating, pallor, weakness, prostration, fast thready pulse, and circulatory collapse Recognition of these types is important not only in order to understand the mortality from bleeding but also in order to institute proper treatment

Mortality Rate from Hemorrhagic Peptic Ulcer —A study of the literature on hemorrhagic peptic ulcer indicates that between 25 and 35 per cent of patients who had peptic ulcer have had episodes of bleeding When all the cases of peptic ulcer are considered without regard to the type of hemorrhage or to treatment, the mortality rate seems low, probably from 1 to 3 per cent in cases of gastric and duodenal ulcer, but two to three times higher in cases of gastrojejunal ulceration However, when the massive type of hemorrhage is studied to determine the mortality rate in this type of case, an entirely different picture is evident, as Allen and Benedict,³ Blackford and Cole,⁶ and Blackford and Williams⁷ have emphasized These observers stated that approximately 50 per cent of patients age 45 or more, who bled from ulcers have had the massive type of hemorrhage, and that 33 per cent of such patients if treated expectantly will die from hemorrhage

Treatment of Bleeding Peptic Ulcer —*Acute Massive Hemorrhage* In acute massive hemorrhage from peptic ulcer, cessation of bleeding occurs

* Read before the American Surgical Association, White Sulphur Springs, W Va , April 28-30, 1941

with rest, blood transfusion, and proper diet in most cases when the patients are less than age 45, and in about 70 per cent of cases when the patients are more than age 45. Obviously, the results from conservative measures cannot be improved greatly by surgical intervention in the younger age-group. The presence of arteriosclerosis, and the difficulty of contraction and thrombosis in an eroded, thickened artery are the probable explanation for the continuation of the bleeding and the higher mortality rate among patients in the older age-groups. The problem which presents itself is how to recognize the 70 per cent of patients who will recover from the effects of the massive hemorrhage under medical treatment, some of whom might die as a result of surgical interference, and conversely, to recognize which of the 30 per cent who die under medical treatment could be saved by surgical treatment. There is a difference of opinion on both phases of the problem between surgeons and internists. One reason for this is due to the fact that an insufficient number of patients who have acute massive hemorrhages from peptic ulcer, have been treated surgically to prove any reduction of mortality in the older age-group by the surgical treatment. Furthermore, there is a great difference between emergency operations performed at the time of, or shortly after, the hemorrhage occurs and several days later, when a nephrotic condition with retention of nitrogen and frequently edema greatly increase the operative risk. Finsterer,¹³ however, reported that he has operated upon 78 patients within 48 hours of the onset of massive hemorrhage. Only four died, a mortality rate of 5.1 per cent. Three deaths (a mortality rate of 4.2 per cent) occurred in the 71 cases in which partial gastric resection was performed, and one death in the seven cases in which gastro-enterostomy was done. Of 74 patients treated later, that is, more than 48 hours after onset of massive hemorrhage, 22 died (a mortality rate of 29.7 per cent). Eleven of the patients who were treated early were between ages 60 and 80. Such a large series has not been reported by any other surgeon, nor have such low figures for operative mortality been obtained. This probably is due in part to the small number of cases in the other series.

Gordon-Taylor^{16, 17} recently reported a mortality rate of 19 per cent (32 cases, with six deaths) in cases of massive hemorrhage in which operation was performed early. Thus, while the value of surgical treatment in acute massive hemorrhage is not proved beyond doubt, on theoretic grounds, at least, eroded arteries in the bases of such ulcers must be attacked surgically among the older patients to reduce the mortality. Finsterer's experience emphasizes the seriousness of a few days' delay in operating upon such patients. The corollary to this seems to be that patients more than age 45 who have massive hemorrhage should be operated upon immediately, that is within 24 to 36 hours after onset of the hemorrhage, or should not be operated upon until they have recovered entirely from the effects of the hemorrhage.

The results of the treatment of acute massive hemorrhage from peptic ulcer at the Mayo Clinic are not entirely clear, largely because of failure in

the past to classify in a separate group the cases of acute massive gastric or duodenal hemorrhage. For the most part, in the past, medical treatment has been employed for such lesions and surgical treatment has been postponed until the patient has recovered fully. When surgical attack has been utilized, it usually has been carried out only after medical measures have failed to control the bleeding. The operative results, in general, are in accord with the findings of others, namely, that operative treatment in the terminal stages has proved relatively hopeless and the more favorable results have been obtained in the few cases in which operation was performed soon after the onset of the hemorrhage.

Chronic Hemorrhage—Treatment of chronic hemorrhage from peptic ulcer is an entirely different problem. Here, interest lies in prophylaxis

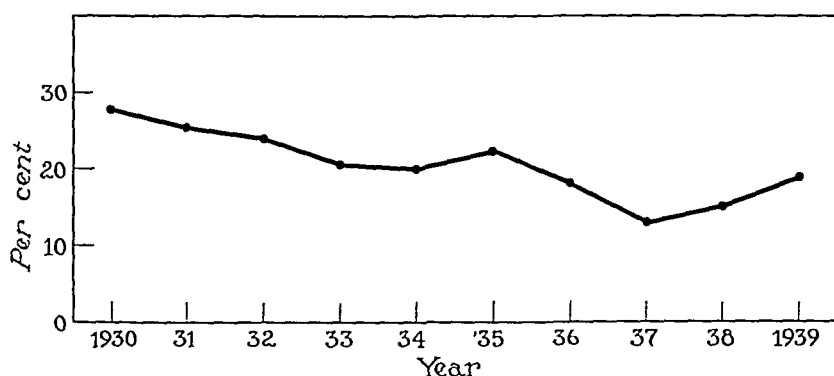


CHART 1—Percentage of patients who had duodenal ulcer treated surgically

against further hemorrhage and relief from intractable symptoms of ulcer. The surgical procedures employed and their indications are of great importance (Chart 1). In cases of bleeding duodenal ulcer, it was formerly thought that gastro-enterostomy afforded protection against further serious bleeding. However, 227 of a series of 336 patients, who had undergone gastro-enterostomy for bleeding duodenal ulcer at the Mayo Clinic,⁵ were traced for seven or eight years after operation. Sixty-six (23.8 per cent) had bled subsequently. In order to evaluate the effectiveness of partial gastrectomy for bleeding peptic ulcers, a study was undertaken of a group of patients operated upon during a five-year period (1932–1936, inclusive).

STUDY OF CASES OF BLEEDING PEPTIC ULCER, IN WHICH PARTIAL GASTRECTOMY WAS PERFORMED AT THE MAYO CLINIC

All the partial gastric resections for bleeding peptic ulcer at the Mayo Clinic, from 1932 to 1936, inclusive, were chosen for study. This period followed the return of one of us (Walters²⁸) from Europe, in various European clinics extensive gastric resections had been observed for peptic ulcer.

Duodenal Ulcer—Partial gastrectomy was performed for duodenal ulcer

in 99 cases, from 1932 to 1936, inclusive, in 42 (42.4 per cent) of these, it was performed for hemorrhagic duodenal ulcer. In the year 1940, at the Mayo Clinic, 138 partial gastrectomies were performed for duodenal ulcer, of which 73 (52.9 per cent) were for hemorrhagic duodenal ulcer (Table I). On the basis of approximately 25 per cent of duodenal ulcers being associated with bleeding, in about 25 per cent of cases of bleeding duodenal ulcers, and 1 per cent of cases of duodenal ulcers without history of gross hemorrhage, partial gastrectomy was performed, from 1932 to 1936, inclusive. In 1940, partial gastrectomy was performed at the Mayo Clinic in about 13 per cent of the cases of bleeding duodenal ulcers, and in about 4 per cent of those of nonhemorrhagic duodenal ulcers (Chart 2).

TABLE I

INCIDENCE OF HEMORRHAGE AND OPERATIVE MORTALITY RATE AMONG PATIENTS TREATED FOR PEPTIC ULCER BY PARTIAL GASTRECTOMY AT THE MAYO CLINIC 1932-1936 INCLUSIVE AND 1940

Lesion	Partial Gastrectomy 1932-1936 Inclusive				Partial Gastrectomy 1940		
	For Hemorrhagic Lesions				For Hemorrhagic Lesions*		
	Total Cases	Cases	Per Cent	Operative Mortality Rate Per Cent	Total Cases	Cases	Per Cent
Duodenal ulcer	99	42	42.4	7.1	138	73	52.9
Gastric ulcer	114	25	21.9	1.2	82	17	20.7
Duodenal and gastric ulcers	37	12	32.4	1.6	8	3	37.5
Jejunal ulcer	87	56	64.4	10.7	42	26	61.9
Total	337	135	40	10.3	270	119	44.1

* Operative mortality rate for 1940 is 4.1 per cent.

Follow-up studies were obtained in 36 of the 42 cases in which operation was performed from 1932 to 1936, inclusive. Prior to operation, there was an average of ten years of uncontrolled ulcer type of pain per patient. Twenty-seven patients gave a history of multiple hemorrhages, 13 of massive hemorrhage, five had hemorrhages within two weeks preceding operation, and six had less than 8 Gm of hemoglobin per 100 cc of blood on admission. Seven of the patients who had had massive hemorrhage were age 45 or more when this occurred. The various types of gastrectomy employed are listed in Table II.

TABLE II

TYPE OF PARTIAL GASTRECTOMY PERFORMED IN 112 TRACED PATIENTS WITH BLEEDING PEPTIC ULCER 1932-1936 INCLUSIVE AT THE MAYO CLINIC

Procedure	Duodenal Ulcer	Gastric Ulcer	Duodenal and Gastric Ulcer	Jejunal Ulcer	Total Cases
Billroth I	7	2	0	10	19
Posterior Polya	28	17	10	30	85
Anterior Polya-Balfour					
Without entero anastomosis	1	0	0	2	3
With entero anastomosis	0	0	0	3	3
Anterior Billroth II	0	1	0	0	1
Posterior Billroth II	0	0	0	1	1
Total	36	20	10	46	112

BLEEDING PEPTIC ULCER

TABLE III

RESULTS OF PARTIAL GASTRECTOMY FOR BLEEDING PEPTIC ULCERS, 1932-1936 INCLUSIVE AT MAYO CLINIC

	Total Cases	Cases Traced	Cases Not Traced	Hospital Deaths	Satisfactory Results			Per Cent	Unsatisfactory Results	
					Excellent	Good	Fair		Number	Per Cent
Duodenal ulcer	42	36	3	3	25	7	2	94.4	2	5.6
Benign gastric ulcer	25	20	2	3	16	2	1	95.0	1	5.0
Duodenal and gastric ulcers	12	10	0	2	7	2	0	90.0	1	10.0
Jejunal ulcer	56	46	4	6	22	6	7	76.1	11	23.9
Total	135	112	9	14	70	17	10	86.6	15	13.4

The results of partial gastrectomy for all bleeding duodenal ulcers show 94.4 per cent satisfactory results (Table III). The results were classified as satisfactory only if there has been no further hemorrhage nor symptoms of ulcer. Results were classed as excellent, when complete relief of symptoms

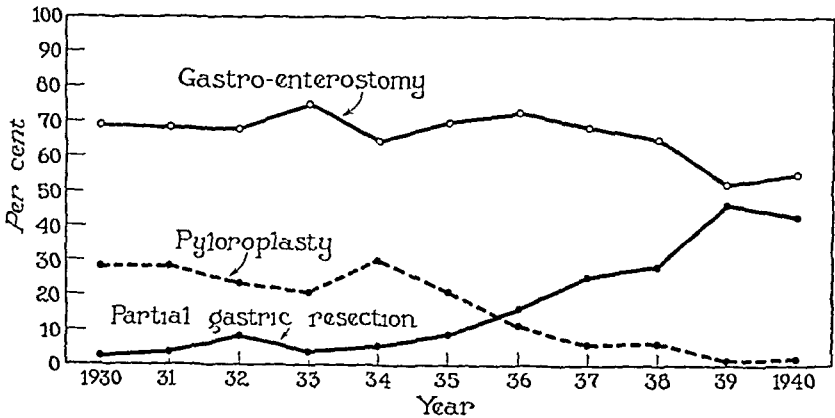


CHART 2—Surgical treatment of duodenal ulcer

was obtained, as good, when relief of the symptoms of ulcer was obtained but occasional fulness or sweating was present after meals, and as fair, when the symptoms of ulcer were relieved but more pronounced fulness after meals, sweating, or occasional vomiting occurred. In no instance did an ulcer type of pain or hemorrhage ensue. Results were classed as unsatisfactory whenever the patient had any ulcer pain or hemorrhage subsequent to operation, irrespective of whether it had occurred once, occasionally, or frequently. Unsatisfactory results were obtained in only two cases (5.5 per cent) in which resection was performed for bleeding duodenal ulcer. In each case, primary posterior Polya-type of partial gastrectomy had been performed without removal of the pyloric antrum of the stomach. Multiple hemorrhages with ulcer type of pain occurred subsequently in both cases.

Gastric Ulcer—From 1932 to 1936, inclusive, about 50 per cent of patients whose condition was diagnosed as benign gastric ulcer at the clinic were operated upon and for about 30 per cent of all the patients who had benign gastric ulcer, partial gastric resection was the operation employed. During this period 114 partial gastrectomies were performed for benign gastric ulcers, of which 25 (21.9 per cent) were hemorrhagic in character.

These statistics are comparable to those for the year 1940, in which 82 partial gastrectomies were performed for benign gastric ulcer, of which 17 (20.7 per cent) were bleeding lesions (Table I)

Two of the 25 patients who were subjected to partial gastrectomy for hemorrhagic gastric ulcer, in the years 1932-1936, inclusive, gave a history of massive hemorrhage. Twenty of these 25 patients were traced. Ninety-five per cent of these 20 patients attained satisfactory results (Table III). In 17 of the 20 traced cases, partial gastrectomy of the posterior Polya-type had been performed, in two, the Billroth I procedure, and in one, an anterior Billroth II-type of resection without entero-anastomosis and with temporary jejunostomy (Table II). Only one patient (5 per cent) had an unsatisfactory result, a posterior Polya-type of partial gastrectomy was performed for syphilitic gastric ulcer (serologic reactions were positive) in this case. There has been no subsequent bleeding but pain of an ulcer-like character has recurred.

Gastric and Duodenal Ulcers—The results of partial gastrectomy for bleeding, concomitant duodenal and gastric ulcers, theoretically, should be comparable to those attained for bleeding duodenal or gastric ulcer. Such was the case in our series. Partial gastrectomy was performed in 37 cases, from 1932 to 1936, inclusive, for concomitant duodenal and gastric ulcers, of which 12 (32 per cent) were for bleeding ulcers (Table I). Of the ten cases of bleeding ulcer traced after partial gastrectomy, satisfactory results were obtained in nine (Table III). In the one case, in which the result was unsatisfactory, a posterior Polya-type of partial gastrectomy was performed. A single, brief period of mild distress and mild hemorrhage occurred after operation, but since then the patient has enjoyed excellent health.

Jejunal Ulcer—Of 87 patients treated by partial gastrectomy, from 1932 to 1936, inclusive, for jejunal ulcer, 56 (64.4 per cent) had associated hemorrhage (Table I). In 1940, 26 of 42 patients (61.4 per cent), treated by partial gastrectomy for jejunal ulcer, had bleeding lesions.

All but seven of the 56 patients who had hemorrhagic jejunal ulcers and were treated by partial gastrectomy, from 1932 to 1936, inclusive, had multiple hemorrhages prior to operation, and 15 had massive hemorrhage. Eight of the patients who had massive hemorrhages were more than age 45 when they occurred. Of the 46 traced patients 30 had been subjected to a posterior Polya-type of resection (Table II).

Thirty-five patients (76.1 per cent) had satisfactory results (Table III). Eleven patients obtained unsatisfactory results. Ten of these 11 had subsequent hemorrhage, and ten had ulcer-type of pain. In six of the 11 cases, in which results were unsatisfactory, the Polya-type of gastrectomy was performed. In four of these, the operations consisted of a posterior Polya resection, and in two of these four cases, the pyloric antrum was not removed. In one case in which the pyloric antrum was not removed, death occurred from massive hemorrhage four years later, and in the other, pain, multiple hemorrhages and proved jejunal ulceration occurred. Of the other two

BLEEDING PEPTIC ULCER

patients who had been subjected to the posterior Pólya-type of gastrectomy, one had a single, mild, subsequent hemorrhage unaccompanied by distress, and one had one subsequent hemorrhage associated with occasional mild distress. In two cases in which results were unsatisfactory, an anterior Pólya-type of partial gastrectomy with entero-anastomosis was performed, in both, multiple hemorrhages and ulcer-type of pain occurred. In five of

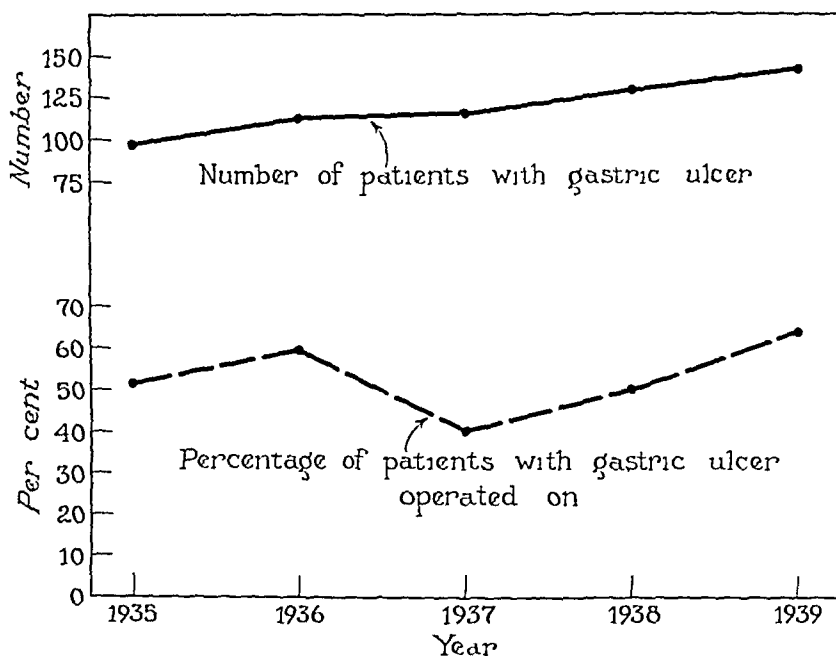


CHART 3 —Percentage of patients who had gastric ulcer treated surgically, from 1935 to 1939

the 11 cases, the Billroth-type of resection was performed, in four, a Billroth I, and in one, a Billroth II. A single hemorrhage and ulcer-type of pain occurred subsequently in the latter case. One patient, who had undergone a Billroth I procedure, had two mild hemorrhages, associated with drinking, these were not accompanied by pain, one had pain without hemorrhage, and the other two, single and multiple hemorrhages with ulcer-type of pain. Interestingly enough, five of the 11 patients reported that they were in good health despite periodic evidence of ulcer.

Analysis of Unsatisfactory Results —Ninety-seven (86.6 per cent) of 112 patients treated for bleeding peptic ulcer by partial gastrectomy, whom we were able to trace, obtained satisfactory results, that is, had no further episodes of hemorrhage or ulcer distress. It is exceedingly interesting to survey briefly the 15 unsatisfactory results (Table III).

Four (26.6 per cent) of the 15 unsatisfactory results occurred in cases in which the pyloric antrum and pyloric sphincter were not removed in the course of partial gastrectomy. In a total of seven of the 112 cases, the pyloric antrum was not removed, and an unsatisfactory result was attained in four of the seven (57 per cent). Both failures in cases in which the

primary resection was for duodenal ulcer, and two failures in the cases of jejunal ulcer presumably occurred on this account

In the early experience with gastric resection, it was not appreciated that the pyloric antrum should be removed in all cases in which gastrectomy was performed for duodenal ulcer. Ogilvie,²¹ out of 22 cases in which the pylorus was not removed at gastrectomy, found six cases of proved jejunal ulcer in a two-year follow-up study. In 100 cases of duodenal ulcer in which the pyloric antrum was removed at partial gastrectomy and in which follow-up study was made 12 years later, there were no recurrent ulcerations and only minor discomfort. Friedmann,¹⁴ in 2,250 gastric resections, found jejunal ulceration in 4 per cent of his early cases and in only 0.5 per cent of the cases in the late group. In the latter group of cases a more radical resection, with removal of the pylorus, was carried out in all instances. The importance of removing the pylorus, if a maximal reduction of gastric acidity is to be obtained, has been confirmed experimentally by Wilhelm,³¹ Crohn,⁹ E. B. Lewis,²⁰ and others (Table IV).

TABLE IV
ANALYSIS OF UNSATISFACTORY RESULTS
(13 per cent of cases)

Procedure or Explanation	Cases	Unsatisfactory Result	
		Cases	Per Cent
Pyloric antrum not removed	7	4	26.6
Entero anastomosis	3	2	13.3
Billroth I	19	4	26.6
Syphilitic gastric ulceration	1	1	
No adequate explanation			
(Resection for gastro jejunal ulcer in three cases)		4	26.6
Total		15*	

* Five of the 15 patients are in good health (three had single mild hemorrhage and two had two mild hemorrhages)

In 72 per cent of cases of duodenal ulcer, all cases of gastric ulcer, and many cases of jejunal ulcer at the clinic, a relative achlorhydria occurs when entero-anastomosis is not performed in association with partial gastrectomy. If entero-anastomosis is performed, marked reduction in gastric acidity is obtained only infrequently. Although a good functional result may not be dependent on a marked reduction of the gastric acidity, when there are unsatisfactory results it is noted that they occur in the group of cases in which a marked reduction of acidity has not followed. A good result was obtained in only one of three cases in which entero-anastomosis was performed as a part of the anterior Polya-Balfour procedure, but in all three cases of gastrectomy with anterior Polya-Balfour anastomosis without entero-anastomosis, results were good.

In four (26.6 per cent) of the 15 cases in which results were unsatisfactory, the Billroth I-type of resection was performed following removal of gastrojejunal stoma for jejunal ulcer secondary to duodenal ulcer.

In a study of the effect of various types of gastric resection on gastric acidity, one of us (Walters²⁶) found that only 25 per cent of patients obtain

relative achlorhydria to the standard test meal after the Billroth I procedure for duodenal ulcer in contrast to 72 per cent after a posterior Polya. It is interesting, therefore, to note that in the present study ulceration has recurred more frequently when the Billroth I-type of resection and anastomosis was employed.

In one case in which results were poor, the patient had a syphilitic gastric ulcer which was associated with hemorrhage, the partial gastrectomy relieved the patient of further bleeding but not of pain.

In the four remaining cases, there was no adequate explanation for the unsatisfactory results, three patients have been subjected subsequently to operation for jejunal ulcer, and one, for concomitant duodenal and gastric ulcers.

Five of the 15 patients, in spite of the classification of unsatisfactory result, are comfortable and report themselves to be in good health, although three had had a single, mild hemorrhage each, one, two mild hemorrhages, and one, one severe hemorrhage. Three also had occasional pain of the ulcer-type.

Operative Mortality—The operative mortality in this study should not be considered as typical, except for the time-period in which the resections were performed. It represents an early period of experience in extensive partial gastric resection for benign ulcerating gastric, duodenal, and jejunal lesions and includes resections in that serious group of 56 cases of bleeding jejunal ulcers. There have been 14 postoperative deaths in the group of 135 cases of bleeding peptic ulcers, a mortality rate of 10.3 per cent (Table III). Three deaths (7 per cent) occurred in the 42 cases in which resections were for bleeding duodenal ulcer. Of the 14 deaths, eight were from peritonitis, five, from bronchopneumonia, and one was sudden, from an indeterminate cause, the third day following a second resection for recurring gastrojejunal ulceration. Two of the eight deaths from peritonitis followed gastric resection for acute ruptured gastric and duodenal ulcers associated with hemorrhage, and one was from peritonitis following resection for hemorrhagic gastrojejunal fistula.

In recent years, with better understanding of the contraindications for partial gastrectomy, and with improvement in preoperative and postoperative care, the operative risk has been reduced considerably.

In 1938,²⁹ there were 215, in 1939,^{18, 22, 27} 352, and in 1940,³⁰ 300 patients were treated by partial gastrectomy for benign lesions of the stomach and duodenum, with a mortality of 2.8, 3.4, and 2.3 per cent, respectively. In 1940, there were 119 partial gastrectomies for bleeding peptic ulcers with five deaths, a mortality rate of 4.1 per cent. All of the deaths occurred in the 73 cases in which resections were for bleeding duodenal ulcer, a mortality rate of 6.8 per cent. Two of the five deaths occurred in cases of massive hemorrhage from duodenal ulcer, in which operation was undertaken more than 48 hours after the onset of bleeding.

SUMMARY AND CONCLUSIONS

Ninety-seven (approximately 87 per cent) of 112 traced patients treated by partial gastrectomy for bleeding peptic ulcer obtained satisfactory results, without further hemorrhages and with relief of the ulcer-type of distress. One patient had a fatal postoperative hemorrhage. If cases in which the pylorus was not removed or in which entero-anastomosis was performed are excluded, then the satisfactory results reach 91.5 per cent. Of the 13 per cent of patients whose results were classified as unsatisfactory, six (54 per cent of the total) were living reasonably normal lives at the time this study was made, although evidence of recurrent ulceration had been present at some period.

Satisfactory results without subsequent hemorrhage or without subsequent ulcer-type of pain were obtained by partial gastrectomy in 94.5 per cent of bleeding duodenal ulcers. All primary resections for bleeding duodenal ulcer relieved the patients except the two in which the pyloric antrum was not removed.

Ninety-five per cent of patients treated by partial gastrectomy for bleeding gastric ulcer obtained satisfactory results. Five per cent had further pain, none had further hemorrhage. In all these cases, entero-anastomosis was not performed and the pyloric antrum was removed at operation.

Seventy-six and one-tenth per cent of patients who had bleeding jejunal ulcers and were treated by partial gastrectomy obtained satisfactory results. Seventy-eight and three-tenths per cent had no further hemorrhage, and one (2.2 per cent) had further pain without hemorrhage. In 88 per cent of the cases of bleeding jejunal ulcer, entero-anastomosis was performed with the gastric resection or the pyloric antrum was not removed, subsequent ulcer-type of pain and bleeding occurred in all. In an additional 88 per cent, Billroth I-type of resection was performed for bleeding jejunal ulcer, and subsequent bleeding and ulcer-type of pain occurred.

The pyloric antrum should be removed in the course of all gastric resections for bleeding peptic ulcer, but entero-anastomosis should not be performed because it tends to prevent a maximum reduction of gastric acidity.

From 1932 to 1936, inclusive, the risk of partial gastrectomy for bleeding peptic ulcer was 10.3 per cent in the 135 cases. In the 42 cases of bleeding duodenal ulcer it was 7 per cent. In 1940, the risk of partial gastrectomy for bleeding peptic ulcer was 4.1 per cent of 119 cases, for bleeding duodenal ulcer it was 6.8 per cent of 73 cases, and there were no deaths among 46 patients who had partial gastrectomies for 17 bleeding gastric, three bleeding gastric and duodenal, 25 jejunal, and one bleeding gastrojejunal colic fistula-type of ulcer. The improvement in operative risk has been attained by improvement in preoperative and postoperative care, the use of chemotherapy, a better understanding of vitamin deficiencies, more rigid indications for partial gastrectomy, and improvement in the postoperative care of pulmonary complications.

Our results support the contention that partial gastrectomy offers the best chance of cure or amelioration of symptoms of bleeding peptic ulcer and the best prophylaxis against further hemorrhage

With elimination of procedures which have proved of least merit, such as failure to remove the pyloric antrum with the resected portion of the stomach, and entero-anastomosis, and with the less frequent use of Billroth I-types of procedures, results should be improved. Thus, in the 119 cases in which resections were performed for bleeding peptic ulcer at the Mayo Clinic in 1940, the pyloric antrum was removed in all but one case, and the posterior Polya-type of resection and anastomosis was employed in 94.1 per cent. The results for 1940 should be superior to the 1932- to 1936-period, when seven pyloric antra were not removed, and only 75 per cent of the partial gastrectomies were of the posterior Polya-type

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DISCUSSION—DR JOHN V BOHRER (New York, N Y) This has been a most interesting and convincing paper on this difficult and controversial question For many years, ulcer therapy has been in a state of flux When it was accepted that peptic ulcer is best treated conservatively, many of the internists and gastro-enterologists failed to differentiate between peptic ulcer as such, and the complications of peptic ulcer It is here that Doctor Walters' paper is of most value

He has shown us a large series of ulcer cases complicated by bleeding These patients have been operated upon, and an adequate follow-up has revealed a very satisfactory result It is certainly most convincing and timely

The statistics presented by Doctor Walters on the acute, massive gastric hemorrhage are of particular interest He stated that in patients above age 45, treated conservatively, there is a mortality between 30 and 40 per cent Our statistics from the Knickerbocker Hospital confirm this figure

Permit me to present some statistics that have been collected both from the Knickerbocker Hospital records and from a questionnaire sent to the members of this Society

During the ten-year period, there were approximately 41,000 patients admitted to the Knickerbocker Hospital, 456 for ulcer, of those 182 for bleeding, and 80 were classified as massive gastric hemorrhage Massive gastric hemorrhage was defined as a patient with two million or less cells, and 35 per cent hemoglobin or less, this being accepted as a base line as no patients died above that level There was a mortality of 17.5 per cent for massive gastric hemorrhage, or 7.6 per cent if computed on the entire bleeding group, or one death in every 3,100 patients admitted

During the last two years, four patients have been operated upon during the bleeding period, two were delayed, and two were operated upon within a 48-hour period All recovered One died of pneumonia ten days postoperatively It is just possible that the

application of chemotherapy in massive doses intraperitoneally might be a prophylactic for postoperative pneumonia

In all, there were 1,556 cases studied. In the hospital group, there were approximately 1,000 cases with a modest mortality of 11.3 per cent. That is probably due to a less rigid classification of massive gastric hemorrhage.

There were 548 patients treated conservatively, with a 16.7 per cent mortality, but those above age 45 in the gastric series had a mortality of 29.3 per cent, while the duodenal group had a mortality of 21 per cent. While it is recognized that the older patients, those above age 45 with massive gastric hemorrhage, have a much higher mortality, your attention is called to those of the gastric series—48 patients with nine deaths, or practically a 20 per cent mortality. Thus we cannot entirely forget the younger patients with gastric ulcers.

One hundred and twelve patients were operated upon with subtotal gastrectomy, with a 17.8 per cent mortality. This line really should read "with 82 per cent living," because most of these patients were operated upon as medical failures.

There were 48 patients operated upon by various operations, such as gastroenterostomy, ligation, local resection, *etc.* Seventeen died, a mortality of 35.4 per cent. Obviously, subtotal resection is the operation of choice.

Seventy-five marginal ulcers were reviewed, with a gross mortality of 8 per cent, 15 were reoperated, three having a subtotal gastrectomy, with one death. Sixty were treated conservatively, with five deaths.

The ulcer that is lethal, if treated conservatively is the one with an open vessel in the center of the crater surrounded by scar and granulation tissue. In most instances, spontaneous cessation is impossible and operation is necessary, within the 48-hour period to prevent a mortality.

DR FORDYCE B. ST. JOHN (New York, N. Y.) May I enter a plea with Doctor Walters to continue the follow-up in these cases indefinitely. We have a dictum in our Peptic Ulcer Follow-Up Clinic, which is now 25 years old, as follows: "Never discharge an ulcer case from the Follow-Up Clinic." Thus, the follow-up record is preserved in continuity. Although, at times discouraging, it has proved most informative. The general excellence of the immediate and late results of subtotal gastrectomy with peptic ulcer, with persistence or complications, is a matter of factual record in any well organized surgical follow-up clinic. We have people, however, in our clinic (now representing a small but real percentage of complications), even after a ten-year follow-up period with no trouble, who have developed symptoms. It is but fair to add, however, that in many of these cases, especially the earlier ones, the actual amount of stomach which has been removed is difficult to determine, and in others, it is evident that a true subtotal gastrectomy has not been performed.

A verbal communication from another large clinic in New York is to the effect that they have had, and are having, a similar experience, and even in some cases where a technically satisfactory subtotal gastrectomy would seem to have been performed.

DR ARTHUR W. ALLEN (Boston, Mass.) In 1933, Doctor Benedict and I published a study of the cases of massive hemorrhage from duodenal ulcer occurring in our hospital. We found that there had been one death in a man, age 25, from hemorrhage, another death in a woman, age 35, and two other males in the late forties had died. These were from a group of 90 patients under age 50.

In 42 patients over age 50, admitted during that same period of time, the mortality rate from hemorrhage was 33.3 per cent.

I have just checked the data from 1933 to January 1, 1941, in our hospital, and found that there have been 80 cases of acute, massive hemorrhage from duodenal ulcer during that eight-year period. Modern methods of treatment, such as feeding the patients early, and administering continuous transfusion, have been employed. There have been nine deaths from hemorrhage in the 80 cases. All of those patients who died were over age 50, except one, and that patient was age 44.

Last week, a man, age 30, on our service, died of massive hemorrhage from duodenal ulcer. At autopsy, an entire segment of the vessel, running behind the duodenum, was found eroded away.

In other words, the mortality rate in the younger patients from hemorrhage is quite low, lower perhaps than we can match by an immediate surgical procedure.

In the older age-group, we have operated upon some of these patients during the early hours of bleeding, seven such patients have survived the procedure, and one died. All patients in this group were beyond age 50, except one. I do not believe we will have the opportunity, in our institution, to prove whether one can operate upon a very large group of acute, massive hemorrhage cases in the younger patients with as low a mortality rate as we have in those operated upon at the time of election.

Our experience with operation upon bleeding ulcers at the time of election corresponds very closely to that of Doctor Walters. Our group has not been so large, but we have learned definitely, namely, that we cannot leave the antrum of the stomach behind without having further trouble. Five out of seven cases treated in our clinic by the "resection for exclusion" method, have developed subsequent ulcers. Fortunately, most of our resections have included the antrum or antral mucosa, and the results have been good, when this has been done.

Doctor McKittrick has been very much interested in "staging" the procedure of subtotal gastrectomy in difficult cases. By dividing the antrum and proceeding with proximal subtotal resection as a first stage, and then deliberately going back six weeks later and removing the pyloric segment. This seems to me to satisfy a great many of the objections to the more radical one-stage procedure on these deeply adherent ulcers during their acute phase or when the inflammatory reaction is so great.

DR ROSCOE R GRAHAM (Toronto, Can.) I was disturbed by Doctor Zininger's suggestion that we are to operate as an emergency upon cases of massive gastric hemorrhage. The survey of our own group revealed 136 cases of duodenal ulcer with the criterion of gastric hemorrhage being an hemoglobin drop to 50 per cent or less. None of these was operated upon. The mortality was 7 per cent. With one exception, I think all the cases that have been operated upon in our own hospital have died when treated as an emergency.

DR JOHN A MCCREERY (New York, N. Y.) I would like to speak for a moment in regard to Doctor Walters' paper, particularly with reference to the marginal ulcers. He has done us a favor in bringing to our attention the importance and frequency of massive hemorrhage in this group of cases.

We are apt to think of marginal ulcers as characterized by intractable pain and, in the late stages, going on to the development of a gastroduodenal fistula. I was surprised at the frequency of hemorrhage in Doctor Walters' statistics, but in looking up my own cases from the First Division of Bellevue, found that 10 per cent of our marginal ulcers had at some time had a massive hemorrhage. I do not agree with Doctor Walters in his preference for the posterior anastomosis, feeling that the anterior route has, at least in my hands, been more satisfactory. It seems to me that with the anterior procedure we can take out more of the lesser curvature, and that a relatively aseptic operation can be performed without clamps, and with perhaps a little less chance of leakage at the anastomosis.

Our experience in follow-up in these cases coincides with that of Doctor St. John, but at Bellevue the question of the economics of follow-up in a city hospital becomes of importance. I have tried to follow-up our gastric cases for seven years, feeling that if we can carry them through that length of time without symptoms we might feel that they were cured. Recently, however, a patient upon whom a gastro-enterostomy had been performed 19 years ago, and who had been followed for seven years in the clinic, came back with a six months' history of pain, and was found to have a marginal ulcer which had developed after 18½ years of complete relief following his gastro-enterostomy, so perhaps we should follow these cases indefinitely.

One point in Doctor Allen's paper which I would like to stress, is the importance of the Wassermann reaction, or rather the importance of not relying on it too seriously. Wassermanns are done as a routine on our Service, but it has been our experience that true syphilis of the stomach is a rare disease, and that gastric lesions in patients with positive Wassermanns have been more apt to be benign or malignant ulcers in patients with syphilis, rather than true syphilitic ulcers.

DR FRANK H LAHEY (Boston, Mass.) These are both very interesting papers, and it seems to me that there is a good deal to be learned from each of them.

To deal with the first one, it is interesting to note in all the clinics the progressive

BLEEDING PEPTIC ULCER

change in the percentage of operative cases. In just short of 5,000 duodenal ulcers, we have operated just short of 7 per cent. In 380 gastric ulcers, we have operated upon 27 per cent. That, I think, represents about the attitude to-day regarding the surgical treatment of ulcers.

There is one thing I would like to relate, based on my own personal experience in the way these cases are operated upon for hemorrhage. There will be a tendency, I think, to undertake conservative types of resections, particularly the Finsterer resection by exclusion, in the cases of ulcers operated upon for bleeding, because these ulcers are active, indurated, and penetrating, and particularly because they are so often close to or adherent to the common duct. Furthermore, they shorten the duodenum and make one think the ulcer is adherent more closely to the common duct than it really is. Until one has had considerable experience in mobilizing these active ulcers, he tends to assume that it would be too dangerous from the point of view of possible injury to the common duct to remove them. This is, I think, a mistake. In very few cases will it not be possible to mobilize these ulcers so that they can be removed, and then the disadvantage of leaving behind the part of the duodenum containing the ulcer or the lower end of the stomach in resection by exclusion of fistula will not occur.

The technical procedure which makes this possible, based upon our experience, is the approach to the duodenum from below the common duct, rather than from above. If you attempt to mobilize the duodenum by approaching it from above, you will be in constant dread of opening the common duct. If you mobilize it well from below, turn it over and demonstrate the common duct from behind, from its posterior aspect where it is not involved in the exudate, it will be possible to remove the ulcer safely leaving a portion of the duodenum, and it can be done in practically all cases.

Let me say, in regard to the antecolic anastomosis without entero-enterostomy, I did this because I admit a jejunal ulcer may occur in the stump of the stomach. If an antecolic anastomosis without entero-enterostomy is done, it will be easy to handle. Furthermore, the idea of not doing enterostomy is a sound one. I can say it can be done safely from the number we have performed.

Our mortality has decreased remarkably. I could not help but think of it when we talked about carcinoma of the colon this morning. The mortality in an operation will decline on one basis, that of a large experience. The whole principle of low mortality rates in these extensive operations of resection of the stomach or of the colon and rectum involves one sound factor, that is that they are difficult operations and they can be made safe only by giving them to a few men to do. If you spread them out, as is true of less serious operative procedures, the mortality will be high, but if you give them to a few men in clinics to do, as they become familiar with them, the mortality will be lowered.

As evidence of the lowered mortality rate, in the first year when we did subtotal gastrectomy for ulcer, our mortality rate was 18 per cent, in the second year it was 11 per cent, and we have now done 154 subtotal gastrectomies for ulcer with but one fatality and that a pulmonary embolus. That these are not selected cases but represent true mortality rates is proven by the fact that included in this group were 36 gastro-jejunal ulcers requiring resection of the jejunum in addition to the subtotal gastrectomy, and three gastrojejunocolic fistulae requiring resection also of the ascending and transverse colon.

I was worried about Doctor Allen's paper, but knowing his sound judgment I should have known better. I was worried that he would take the position that every gastric ulcer should be resected. That I think is a dangerous position, and the mortality from promiscuous resection would be high. After listening to his paper, I would agree with practically everything he said. I think it is very sound in principle, and I think all of these criteria are sound, and by them we may improve the results in resections for carcinoma of the stomach, which to-day are, of course, so distressing to us all.

DR M. M. ZINNINGER (Cincinnati, Ohio). It has been a great privilege to hear Doctor Walters' paper which shows so clearly that bleeding ulcer can be so satisfactorily treated by resection, a fact which many of us have believed, but which we have not been in a position to prove statistically. With his large series and excellent follow-up, he has been able to show it. My experience with bleeding ulcers has, of course, been much smaller than Doctor Walters', but, in general, it agrees closely with his. At Cincinnati, we see a good many patients with bleeding ulcer who enter the hospital.

during or immediately following a massive hemorrhage, and it is about the management of this type of case that I wish particularly to speak. During the period 1933-1936, 33 such cases were admitted to the Cincinnati General Hospital. None was operated upon during the period of active bleeding. Six died of uncontrolled hemorrhage, a mortality rate of 18 per cent. During the years 1937-1940 inclusive, 92 patients were admitted with massive hemorrhage diagnosed as due to bleeding ulcer with ten deaths, a mortality rate of 10.87 per cent. We believe that the reduction in mortality rate during the second of these periods was due to better medical management, plus the fact that some of the patients were operated upon during the period of active bleeding and the bleeding controlled surgically. Though it has been shown that operation is a life-saving procedure in some of these cases, the selection of patients and the choice of time for operation are points which are not yet entirely agreed upon. Many of our patients had not been under observation before they came in with acute hemorrhage, and often the source of bleeding could be determined only with difficulty. We have made use of roentgenograms by the Hampton technic in this sort of case when bleeding persists, and recommend operation if an ulcer can be demonstrated. In cases with known ulcer who have been under treatment, we believe that if massive hemorrhage occurs, operation should be carried out promptly, not waiting for a second or third hemorrhage, especially if the patient is age 45 or older. Table I shows my personal experience with the surgical treatment of such lesions during the past four years.

TABLE I

Cases	Color Sex Age	Operation No of Days after Adm	In Shock No of Times	Procedure	Result
1	W M 58	50	5	Ligation of vessels entering gastric ulcer	Well 1 yr
2	W F 41	13	3	Ligation of vessels entering gastric ulcer	Died 2½ mos Acute liver atrophy
3	W M 54	2	2-	Partial gastrectomy for duodenal ulcer	Well 2 mos
4	B M 29	7	3	Partial gastrectomy for duodenal ulcer	Died on table
5	W M 53	2	2	Partial gastrectomy for gastric ulcer	Well 2 mos
6	W M 60	3	4	Partial gastrectomy for duodenal and gastric ulcer	Died 14 days Pneumonia Finally ceased bleeding
7	B M 67	14	Almost continuous	Bleeding point not found	Well 3 mos

As can be seen, some of the gastric ulcers were treated by ligation of vessels, others by resection, while all duodenal ulcers were resected. Only two were operated upon within 48 hours of admission, both of whom recovered. The second case probably should not be included, as it seems likely that this was a carcinomatous rather than a simple ulcer, since a Kruckenberg tumor of the ovary was removed from this patient about two months later. The seventh patient also should not properly be included because no ulcer was found and the bleeding was not controlled surgically. He is included here because he was operated upon with the preoperative diagnosis of bleeding duodenal ulcer.

In addition to these cases—only five of which were proven ulcers—three others were operated upon by members of the resident house staff during this same period. All three of these died, one of pneumonia on the fourth day, the other two on the operating table. Death on the table is a most unfortunate accident, which indicates either too long a preoperative delay or poor judgment in selection of cases.

Three slides were here shown of drawings of resected specimens showing the thick-walled vessel in the base of the ulcer, with the eroded hole in the vessel plugged only

with a soft blood clot—the same type of lesion as is seen in cases at autopsy after uncontrolled bleeding. It seems clear to me that with such a pathologic condition present, spontaneous cessation of bleeding cannot be expected to occur regularly, and that in some of these cases, operative control of the hemorrhage will be necessary. The high mortality in our group of patients with operation, we believe, is due to the fact that we have not had an opportunity to operate as early as we would have wished, but only after conservative treatment had been found to be ineffectual. We believe that all these patients operated upon with ulcer would have died of uncontrolled hemorrhage without operation.

DR WALTMAN WALTERS (Rochester, Minn., closing) Eight years ago, it was more or less accepted, I believe, although a few physicians did not agree, that a trial course of medical treatment should be instituted in all cases of gastric ulcer. I am very happy to see that opinion change. The reason for this change, I think, is recognition of the fact that a carcinomatous lesion is present in a definite percentage of cases in which the roentgenologist makes a diagnosis of gastric ulcer.

A review of all our cases of cancer of the stomach in which operation was performed from 1907 to 1938, inclusive, has been made at the clinic, and two very interesting findings, among others, have come out. The first is that in 10 per cent of the cases of malignant lesions of the stomach in which resection was performed, the lesion had been reported by the roentgenologists to be gastric ulcer. Although the presence of a gastric lesion was recognized on roentgenologic examination in 99 per cent of cases in the series, recognition that it was a definite cancer was possible in only 75 per cent of the cases. These same statistics held for 1939, except that in 7 per cent of cases of cancer of the stomach in which resection was performed, a diagnosis of gastric ulcer had been made on roentgenologic examination.

The most disastrous observation in regard to symptomatology in our 1907–1938 series, was that 30 per cent of the patients gave a history of an ulcer type of distress, and of this 30 per cent, 80 per cent, or four-fifths, responded to medical treatment.

GASTRIC ULCER*

THE SIGNIFICANCE OF THIS DIAGNOSIS AND ITS RELATIONSHIP TO CANCER

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FROM THE MASSACHUSETTS GENERAL HOSPITAL BOSTON, MASS

GASTRIC AND DUODENAL ULCER have been discussed so frequently under the general heading of "Peptic Ulcer" that a serious confusion has resulted regarding the proper management of these two distinct entities. Early symptoms in both diseases are much alike and the conservative measures, found adequate in uncomplicated duodenal ulcer, will also be temporarily effective for gastric ulcer. The greater frequency of acute duodenal lesions, compared to those in the stomach, has enhanced the standardization of the treatment of duodenal ulcer. This regimen applied to the more rare gastric ulcer has often proved disastrous. We believe that the time has come for a clarification of our ideas concerning the management of gastric ulcer and that every effort should be made to stress the seriousness of this lesion.

The difficulty in the differential diagnosis between ulcer and cancer of the stomach in our clinic has impressed us so forcibly that we feel justified in reporting our experience concerning the matter. We had already formed some ideas from certain cases falling into our hands for treatment but were surprised to find the evidence so clear to us when the available material was evaluated. The records of all patients, treated in our hospital during the ten-year period ending January 1, 1940, who have had the diagnosis of gastric ulcer, have been carefully analyzed for this purpose.

TABLE I
GASTRIC ULCER
Error in Diagnosis of Cancer

	No. of Cases	Per Cent
(A) Entire group		
Original diagnosis ulcer	277	
Final diagnosis cancer	39	14
(B) Patients treated medically*		
Original diagnosis ulcer	175	
Final diagnosis cancer	13	7.4
(C) Patients treated by gastro enterostomy		
Postoperative diagnosis ulcer	23	
Cancer proved by follow-up studies	4	17
(D) Patients treated by resection*		
Preoperative diagnosis ulcer	69	
Cancer proved histologically	30	43

* Several patients are included in both groups B and D

This study deals with 277 patients whose original diagnosis was gastric ulcer (Table I). Thirty-nine of them, or 14 per cent, finally proved to have

* Read before the American Surgical Association, White Sulphur Springs, W. Va., April 28, 1941

cancer Seventeen cases with a preoperative diagnosis of cancer proved to have benign ulcer This makes a total of 255 cases of ulcer for analysis (Table II) The diagnostic methods were the usual ones employed in a large general hospital The clinical diagnosis was based on the history, physical examination, and the laboratory data, this was confirmed by roentgenographic studies in all cases and by gastroscopy in many of them When the ulcer was a large one or in one of the areas of the stomach where cancer is more likely (Fig 1), or if there had been a poor response to conservative treatment, the patient was usually transferred to the surgical department

In evaluating the percentage of error in diagnosis, each opinion was given its *pro rata* credit and no case, whose combined preoperative diagnosis was less than 50 per cent in favor of one diagnosis, was used in arriving at the diagnostic error The opinion of the pathologist was accepted as final In 69 cases subjected to gastric resection with a preoperative diagnosis of ulcer, 30, or 43 per cent, had a final diagnosis of cancer In 18 of these patients, the error was made by all observers In the remaining 12 cases, there was an opinion favoring the diagnosis of ulcer in from 50 to 90 per cent of those

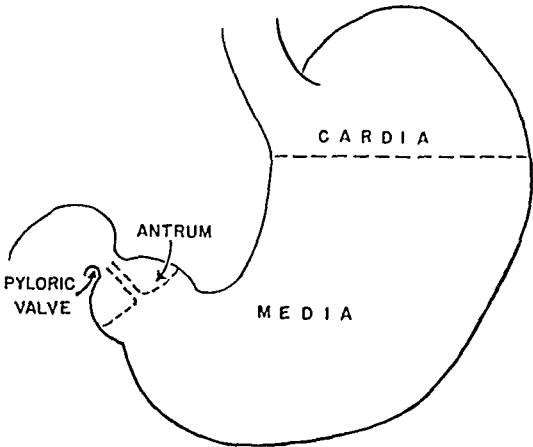


FIG 1—Anatomic divisions of the stomach

TABLE II
GASTRIC ULCER 1930-1939
Massachusetts General Hospital

Final Diagnosis Ulcer*	Cases	Deaths	Patients Dying in Hospital (Per Cent)
Medically treated			
1930-1934	59	3	5.1
1935-1939	103	4	3.9
Total	162	7	4.3
Surgically treated (acute perforations excluded)			
1930-1934	62	8	12.9
1935-1939	31	2	6.4
Total	93	10	10.7
Total cases	255	17	7.5

* The original diagnosis of cancer was made on 17 of this group

who participated in the management of the problem If one wishes to take the most optimistic attitude and work out the percentage values on the basis of including only half of those cases where there was some divided opinion, the result is bad enough, since it is at best a 35 per cent error

We have all performed radical gastric resection under the diagnosis of

cancer, only to have the pathologist bring us the good news that the lesion proved to be benign ulcer. In the same decade of this study, 344 cases with a preoperative diagnosis of cancer that were either resectable or upon whom a palliative operation was possible, there were 17 with a final diagnosis of benign ulcer—a diagnostic error of 5 per cent. If we take our percentage error in both groups of cases into consideration, we still have much to be desired in the more favorable lesion for cure.

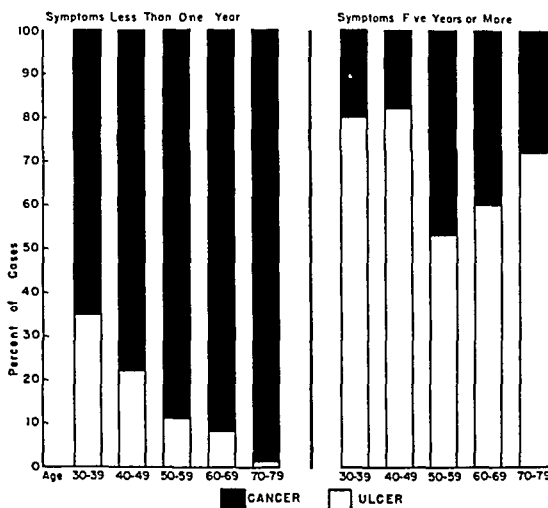
In 175 patients treated medically under the diagnosis of ulcer, 13 were eventually proven to have cancer—a diagnostic error in this group of 7.4 per cent. Twelve of them finally came to operation after an average interval of ten months from the original observation.

During the period covered in this report, 23 patients with gastric ulcer were treated by conservative surgery, usually gastro-enterostomy, with or without cauterization of the ulcer. Four of these patients later died of cancer, thus illustrating, more graphically, the difficulty of the surgeon to make a true diagnosis when the lesion is actually under observation. This is also a very strong argument in favor of partial gastrectomy when gastric ulcer is subjected to any surgical procedure.

Naturally, we have concerned ourselves with the reasons for our high percentage of diagnostic error when dealing with gastric ulcer. These factors were studied as follows: (1) The age of the patient and the duration of symptoms, (2) the location of the lesion, (3) the size of the ulceration, (4) the hydrochloric acid level of the gastric contents, (5) the rate of healing under medical therapy, and (6) the type of pain or discomfort complained of by the patient.

We expected to find that patients complaining of indigestion, hyperacidity, and gaseous eructations for the first time after age 50, would have cancer rather than ulcer. These data are illustrated in Graph 1. Here, we see that this is an important diagnostic point, since patients beyond the fifth decade, with a gastric ulceration causing symptoms of less than one year, are over five times as likely to have cancer as ulcer. On the other hand, those patients with symp-

COMPARISON AGE AND DURATION OF SYMPTOMS
GASTRIC ULCER & CANCER

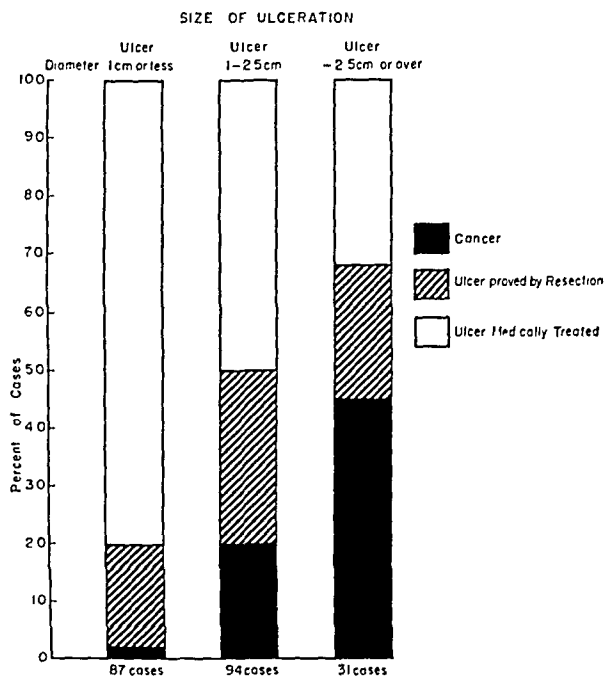


GRAPH 1

toms of five or more years have exactly the reverse ratio of ulcer to cancer. It seems evident to us, then, that conservative therapy in this older age-group has little to support it, nor is the incidence of ulcer in any group of cases great enough to make one certain he is not dealing with cancer.

That ulcerative lesions in some locations in the stomach are more likely to be cancer has been well-established. Holmes and Hampton¹ have previously stressed this point. In the group of cases under discussion, we have represented the percentage values in Figure 2. We have no difficulty in making up our minds regarding the treatment of ulcerative lesions arising in the fundus and in the prepyloric regions of the stomach, since the chance of cancer so far outweighs the risk of surgery. In the more common site on the lesser curvature, where 50 per cent of all gastric ulcers occur, we have been prone to feel safe on the basis that most of these lesions are benign. However, we actually find many of our mistakes in diagnosis are in lesser curvature ulcers. Thus, the physician, believing that this peptic ulcer will behave like others, fails to take into consideration the possibility of cancer. He then neglects to keep such a patient under observation until the lesion is completely healed, and he often is not actually aware of the true situation until the opportunity for cure is entirely lost.

The size of the ulceration is of some importance, and this is illustrated in Graph 2. In only two of our cases, with final diagnosis of cancer, was the lesion under 1 cm in diameter. The incidence of cancer increases progressively with the diameter of the ulcer. The majority of lesions over 2.5 cm in diameter, proved by resection, turn out to be carcinoma. Between the diameters of 1 to 2.5 cm, the margin of error is such that not so much importance can be attached to the size. The average diameter of the benign lesion was 1.7 cm, while those showing cancer averaged 2.3 cm. The size of the crater, then, although of some help in the differential diagnosis, is not a reliable guide. The margin of error is exactly 50 per cent in ulcerations of 2 cm in size. One huge ulcer requiring total gastrectomy proved to be benign.



GRAPH 2

The hydrochloric acid level has been taught for years to be an important differential diagnostic guide in gastric ulcerations. This is illustrated in Graph 3. Here, we see that acidity and cancer are compatible. An occasional benign ulcer will have achlorhydria, but it is clear that one should not often stress this possibility. It will be observed that the percentage of cases with free acid in the stomach is just as high with "ulcer-cancer" as it is with benign ulcer. There has been far too much emphasis on the acid

levels in relationship to the innocence of the lesion. A gastric analysis, negative for acid, is of help, but one with acidity is of no aid in the differential diagnosis between benign ulcer and cancer.

APPROXIMATE INCIDENCE OF CANCER IN GASTRIC ULCERATION

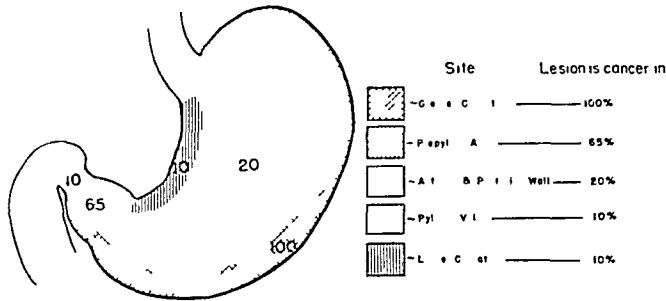
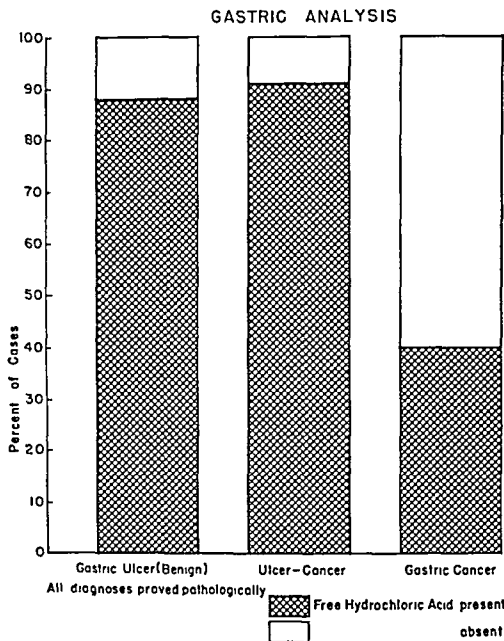


FIG. 2

The rate of healing of gastric ulcers under medical supervision has interested us. Although it is not possible to graphically illustrate such a study, we have been able to form some opinion concerning it. In order to get a

base-line in regard to healing, we believe it is important that all patients with gastric ulcer should be admitted to the hospital for treatment, where conditions for cure can be made ideal and failure of the lesion to heal becomes of real significance. Too often, these patients are given the ambulatory advice handed out with impunity to patients with duodenal ulcer. The individual loses his symptoms and fails to return for a check-up. The physician then often interprets the absence of pain as such a favorable sign that he fails to insist on roentgenologic and gastroscopic confirmation of healing. Even when this is done, the report usually indicates a diminution in the size of the ulcer, and the impression is not made upon the patient regarding the im-



GRAPH 3

importance of observations until complete healing has taken place. We have operated upon one patient with cancer and involved lymph nodes in a lesser curvature ulcer that completely healed after two months of medical therapy, according to roentgenographic and gastroscopic examination. Thus, it seems to us important that these patients should be followed under ideal hospital

management until complete healing has occurred. Even this cannot be construed as certain proof that the ulcer is benign, and such a healed ulcer should be again observed after a month's time as any evidence of recurrence demands surgery. If this program were insisted upon in this group of patients, a considerable number could be spared death from cancer. Of course, it is impossible to make a rule regarding the length of observation justifiable in all cases. We do feel however that, under proper conditions in the hospital, one should expect complete healing in one month if the lesion is benign.

The type of pain an ulcer of the stomach produces is not of as much importance as we thought it might be. We were of the opinion that the more vague the symptoms of indigestion, the more likely the lesion would prove malignant. Also, patients who have uncontrollable pain on a strict diet often prove to have cancer. On the other hand, it has been proved repeatedly that a decrease in the amount of pain occurring under treatment does not indicate that the ulcer is benign.

Although the physician is willing for his patient to submit to surgery, if he is convinced that the lesion is cancer, it is hardly to be expected that he should trust the surgeon with a benign ulceration of the stomach. This attitude has been brought about by the surgeon himself, since he has been slow in developing a sound surgical procedure for such lesions. Also, it has taken time and experience to evaluate methods that seemed in the beginning, for one reason or another, to offer cure in the majority of cases operated upon. The morbidity and mortality in this field of surgery has brought about a natural reaction on the part of physicians to evade the surgeon if possible. We believe now that we have evidence to warrant making a fresh endeavor to convince our medical colleagues that gastric ulcer should be fundamentally a surgical disease. We are willing that he continue to treat early, small ulcerations in the safer zones within the stomach, particularly in the younger patients. We do feel, however, that his treatment should be on a different basis than that used in duodenal ulcer. He should follow the patient with gastric ulcer until the lesion is completely healed and then check by roentgenograms and gastroscope at frequent intervals. He should be suspicious of any lesion that tends to recur or one that heals imperfectly within a short period of time. If he would take this attitude, in order to allow his patient to have an early and favorable operation for cancer alone, he would be justified in his position in the matter.

Under this regimen, a certain number of patients would have gastric resection for benign ulcer. Can the surgeon justify himself on this score? Our mortality figure of 6 per cent in a group of 53 primary resections may be representative since these are from a large teaching hospital where many minds and many hands enter the picture (Tables III and IV). It is necessary to train surgeons and we do not defend such a mortality rate on any other basis. Personal series show even better results as do those from private clinics. There have been no fatalities in 36 resections for gastric ulcer in

our own personal cases, but this is beside the point. The internist must anticipate morbidity and mortality and the surgeon must be able to offset these difficulties if he makes a bid for these cases. In the 51 survivors from primary subtotal gastrectomy for gastric ulcer, we have only two patients

TABLE III
GASTRIC ULCER—SURGICAL THERAPY (M G H 1930-1939)
(Acute Perforations Excluded)

	No of Cases	Deaths	Mortality (Per Cent)
Subtotal resection	56	5*	8.9
Posterior gastro enterostomy	22	3	13.6
P G E plus local excision	7	1	14.3
Local excision	6	1	16.7
Pyloroplasty plus excision	1	0	0
Total gastrectomy	1	0	0
Total	93	10	10.7

* Two deaths occurred in patients who had had previous gastric surgery.
Mortality of primary subtotal resection is 6 per cent.

TABLE IV
GASTRIC ULCER—SURGICAL THERAPY

	Resections	Other Operations	Total Cases	No of Deaths	Mortality (Per Cent)
1930-1934	30	32	62	8	12.9
1935-1939	26	5	31	2	6.4

who have had recurrent symptoms. This is worthy of note when we consider the morbidity frequently associated with prolonged conservative treatment. At least 12 per cent of the patients under observation for gastric ulcer have had continued or recurring symptoms. Therefore, we feel that the results of proper surgery for gastric ulcer justify that form of therapy. This agrees with the conclusions of St. John, *et al.*,² based on meticulous follow-up data and of Walters and Clagett.³

Perhaps the strongest argument in favor of gastric resection for ulcer is based on the comparative data in Table V. In a group of 93 patients subjected to gastrectomy for cancer between 1932 and 1936, reported by Parsons and Welch,⁴ from our clinic, we have an operative mortality rate of 25 per cent. Including these operative deaths, there were 20 per cent of five-year cures. In the small series that we can end-result, there were 30 gastrectomies performed under the diagnosis of benign ulcer—all of whom proved to have cancer. The operative mortality in this group was 10 per cent, and including these deaths, the five-year rate of cure was 40 per cent (Table V). Although we realize that the percentage values in so few cases are open to criticism, we believe it is fair to call attention to the likelihood of a lower mortality rate and a higher cure rate if the resection has been undertaken on the assumption that the lesion is ulcer and not cancer. In other words, the more

benign the lesion appears, the more likely the final cure. It is important to point out in this connection that the surgeon must have in mind the possibility of malignancy when carrying out gastrectomy for ulcer. The operation carries no more risk if the omentum and the lymph nodes of the lesser curvature are included in the resection. If this attitude is adopted in all questionable cases, the cure-rate will be even higher than 40 per cent in those having these early malignant lesions. This opinion is based on the fact that the nodal areas were not included in the resections for ulcer performed between 1930 and 1936.

TABLE V
PROGNOSIS OF GASTRIC CARCINOMA
All Cases of Resected Cancer Preop Diagnosis Ulcer
(1932-1936)* (1930-1939)

Number of cases	93	30
Operative mortality	25%	10%
Five-year curability rate†	20%	40%

* Previously published

† This is calculated from years 1930-1936 and includes operative deaths

We recommend immediate surgery for any one of the following indications—if

(1) The ulcer is of short duration and the patient is over fifty years of age

(2) The ulcer is over 2.5 cm. in diameter

(3) There is no free hydrochloric acid in the stomach

(4) The ulcer is in the greater curvature or in the prepyloric region

(5) The ulcer is chronic and on the lesser curvature

We recommend hospital observation and treatment for one month—if

(1) The ulcer is acute and in a young patient

(2) The ulcer is under 1 cm. in diameter

(3) The ulcer is on the lesser curvature or the anterior or posterior wall

If healing is complete in one month, repeat observations should be made one month after discharge from the hospital.

If healing is not complete in one month, by roentgenologic and gastroscopic examinations, then surgery is advisable.

CONCLUSIONS

Gastric ulcer is, fundamentally, a surgical lesion. This is the direct antithesis of our present concept regarding duodenal ulcer.

Gastric ulcer cannot be distinguished from cancer in a high percentage of cases.

The gastric cancers that simulate gastric ulcer comprise an especially favorable group for cure. On this basis alone, surgery should be the treatment of choice.

The end-results of gastric resection for ulcer seem to substantiate this same form of treatment even if the ulcer is proved to be benign.

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DISCUSSION—DR RALPH COLP (New York, N Y), The logical viewpoints expressed by Doctors Allen and Welch in their excellent presentation will probably meet with the full approval of those interested in this subject. Gastric ulcer, aside from its serious complications of hemorrhage, penetration, and perforation, presents the added hazard of the possibility of carcinoma, and the less likely danger of a carcinomatous transformation of an ulcer. Klein states the latter occurred only twice in a careful pathologic study of 141 cases of chronic ulcer.

In 1936, Dr Percy Klingenstein reported all cases of chronic gastric ulcer, 165 in number, which were operated upon during a ten-year period (1925-1935) at the Mount Sinai Hospital, New York. The majority of patients gave a long-standing history of ulcer symptoms which ultimately failed to respond to medical therapy. There was a smaller group with an acute history, manifested by serious bleeding in 25 instances, and by signs of impending perforation in others. In over 20 per cent of these cases, a diagnosis of carcinoma was made by the roentgenologist and 12 per cent, in which a benign lesion had been diagnosed clinically, were subsequently proven to be malignant.

For purposes of discussion, these ulcers may be grouped into those occupying the pyloric and prepyloric region, those situated at or near the reentrant angle and on the posterior wall of the stomach, and those located in the cardia. The lesions in the latter group of 29 cases were situated well proximal to the reentrant angle and some were *juxta-esophageal*. Many of these, as well as others, were complicated by adhesions to or penetration into the pancreas. A subtotal gastrectomy with removal of the ulcer was performed in 158 cases. The operative mortality was 15 per cent, contributed to mainly by cases with acute and serious gastric hemorrhages, by those with lesions in the cardia, and by those complicated by either previous gastric procedures, or long-standing pyloric stenosis.

During the past three and one-half years, Doctor Klingenstein and I have operated upon 28 consecutive cases of gastric ulcer. There were six other cases in which a benign lesion was suspected but in which a malignant one was found at exploration. We were not forced to operate upon any case with hemorrhage in the acute stage. We made it a rule to explore all prepyloric ulcers because, clinically, it is extremely difficult to differentiate between ulcer and carcinoma in this region. However cases with pyloric stenosis were not operated upon until the blood chemistry determinations were normal.

A subtotal gastrectomy was performed in 23 cases, and a palliative gastric resection without removing the cardiac ulcers, the procedure advocated by Madelener and Florcken, was performed in five instances.

No one will deny that most gastric ulcers respond favorably to medical treatment, but, unfortunately, some malignant lesions, too, grow smaller under rest and appropriate diet. But in all cases, if certain well known and established criteria have not fully satisfied either clinically, roentgenologically, and by gastroscopic examination, after a three-week period of an ulcer cure, then surgical exploration should be insisted upon.

Subtotal gastrectomy is undoubtedly the operation of choice. It removes the ulcer radically, and if the case proves malignant, the chances of cure may be materially enhanced. Penetrating *juxta-esophageal* and high-lying ulcers, even if they do not respond to medical treatment, should be explored, but not radically resected. If they prove malignant, they are inoperable at this stage, and if they are benign, they will disappear following a palliative gastrectomy. The operative mortality in subtotal gastrectomy will be

reduced if these high-lying lesions and cases with acute hemorrhage are treated more conservatively

The follow-up results in gastric ulcer are excellent, and are superior to those obtained from subtotal gastrectomy for duodenal ulcer. No recurrent gastric or gastrojejunal ulcers have been observed.

DR WALTMAN WALTERS (Rochester, Minn.) The objections to a routine medical regimen in all cases of gastric ulcer are that in some of them the lesion, instead of being a small gastric ulcer, is in reality an ulcerating carcinoma, and in others the medical regimen has little effect on the ulcer. In about 10 per cent of cases, roentgenologic or gastroscopic examinations will not assist in the differential diagnosis between a malignant and a benign gastric ulcer. It has been said that a trial course of medical treatment serves as a diagnostic aid, for, if the patient is relieved of symptoms, if roentgenographic examination demonstrates that the ulcer has disappeared, and if blood disappears from the stools, then the lesion is benign. Clinical experience, however, has demonstrated that in some cases of malignant gastric ulceration these criteria may seem to be satisfied but that the lesion does not heal, it only *seems* to have done so, for, as Schindler has shown, the carcinomatous process may extend from the margin of the ulcer into the crater, obliterating it.

The incidence of malignant changes in gastric ulcers has been stated to be from 10 to 20 per cent. Walton said that the statistics of Stewart now are generally accepted. He concluded that in 9.5 per cent of cases chronic ulcer becomes carcinomatous and that carcinoma originates in a chronic ulcer in 17 per cent. Katsch, however, reported an incidence of 20 per cent. Finsterer found that in 532 cases of resection for gastric ulcer the ulcer was carcinomatous in 141, an incidence of 20.9 per cent. In the 1907-1938 series, reported from the Mayo Clinic by Doctors Walters, Gray and Priestley, 10 per cent of the carcinomata were reported as gastric ulcers and 1 per cent as benign lesions.

The risk of the operation for gastric ulcer should not exceed a maximum of 5 per cent, and it is possible to operate upon a large series of patients who have gastric ulcer with a mortality rate of considerably less than 5 per cent. In point of fact, in 278 cases in which partial gastrectomy was performed at the Mayo Clinic in 1939 for benign ulcers of the stomach or duodenum, the mortality rate was 4 per cent. Partial gastrectomy for gastric ulcer was performed in 89 cases, with a mortality rate of 2.2 per cent. In 1940, partial gastrectomy for gastric ulcer was performed in 88 cases, with one death. Excision or gastro-enterostomy or both were performed in 17 cases, with no mortality. The cases were selected carefully, and partial gastrectomy was performed only when the nature of the lesion and the condition of the patient warranted this procedure.

On reviewing 272 cases of chronic gastric ulcer in which operation was performed at the Mayo Clinic from January 1, 1933, to December 31, 1936, inclusive, Clagett and I found that 66.9 per cent of the ulcers were at or above the incisura angularis, 15 per cent were on the posterior wall, and 1.5 per cent were on the greater curvature. The remainder were below the incisura angularis.

In several of the cases at the clinic the ulcer appeared, on roentgenologic examination, to be located very high on the lesser curvature, and for this reason it was thought that operative removal would be difficult, it was found at operation, however, that perforation of the lesion to the capsule of the pancreas had given an erroneous idea of the amount of the stomach between the ulcer and the esophagus. In these cases there was actually much more uninvolved stomach than the roentgenogram indicated. On other occasions, the early division of the gastrohepatic omentum at a very high level assisted in mobilizing the upper part of the stomach so that unusually high lesions could be removed without too great difficulty.

During 1938 and 1939, at the Mayo Clinic, in 26 cases partial gastrectomy was performed for cardial gastric ulcer, with one death, a mortality of 3.8 per cent.

I have referred to these cardial ulcers because frequently I have seen patients with such lesions in whom the excuse for a course of medical treatment, even though the lesion was large, and in many cases had been complicated by hemorrhage, was that the lesion was probably located too high to be removed safely. The fallacy of this opinion is borne out not only by the fact which has been brought out, namely, that the lesions appear roentgenographically to be higher than they really are, but in a group of cases in which

such lesions were removed surgically, the operative mortality was only slightly higher than that for similar operations for gastric ulcer located at the lower levels on the lesser curvature or the body of the stomach

In regard to some of the points on technic brought out in the discussion of Doctor Allen's paper, I sincerely believe that as time passes and anterior anastomosis after resection is performed in more cases, experience will show that posterior anastomosis is preferable in cases in which resections are performed for duodenal ulcer. My reason for this statement is my experience abroad, where many more resections have been performed for duodenal ulcer and the posterior method has proved the method of choice. Furthermore, in my own experience in cases in which the anastomosis is necessarily made anterior to the colon, because of the longer loop of jejunum used in the anastomosis, retention in that proximal loop develops in a definite percentage of cases, and entero-anastomosis has to be performed later. This procedure interferes with some of the physiologic-chemical effects of the operation, so that the reduction of gastric acidity is not as great. You will recall that 25 per cent of the unfavorable results in resections for bleeding ulcers which I reported were in cases in which entero-anastomosis was performed.

Theoretically, the Billroth I-type of operation should be an excellent type of operation. In selected cases of carcinoma, its results have been excellent and similar results can be expected when it is used in the treatment of gastric ulcer. When employed in the treatment of duodenal ulcer, it fails to produce a relative achlorhydria in 75 per cent of the cases, and the incidence of recurring duodenal ulceration is high. For example, on follow-up study in our series of bleeding ulcers, recurrent bleeding ulcers were found in four of 19 cases in which the Billroth I-type of anastomosis was employed. In 26.6 per cent of the 15 cases in the whole series, in which results were unsatisfactory, the Billroth I-type of anastomosis had been employed. It is true that these poor results occurred after resection for jejunal ulcers. It might be assumed that the Billroth I-type of anastomosis is the best type in such cases, but such has not been my experience. I have performed Billroth I resections in many cases for duodenal ulcer, gastric ulcer, and gastric carcinoma. The incidence, in my experience, of recurring ulcer after this type of operation performed for duodenal ulcer has been comparable to that following gastro-enterostomy. On the other hand, in the treatment of selected cases of gastric ulcer or gastric carcinoma it has a definite place and the results are equally as favorable as those from the Polya-type of operation.

DR FORDYCE B. ST. JOHN (New York, N. Y.) We are in complete accord with Doctor Allen's conclusions, in that we feel they represent a definite tendency in the right direction based on appreciation of potential dangers in ulcer of the stomach which are all too often missed until too late. We have had similar experiences because of our own errors in diagnosis, and that of our medical friends, the roentgenologist and the gastroscopist.

The newer problem of antral gastritis has introduced an "X" factor which may furnish potential danger in differential diagnosis.

Aside from these factors of danger, we should remember that, fundamentally, we are dealing in carcinoma of the stomach with a lesion, advanced on admission to most of our clinics, and in which, in the study of the biologic characteristics of this tumor, one must realize that about 66 per cent are of the invasive type, difficult to cure under any circumstances, and only about 33 per cent are of the so-called fungating type, or the more favorable lesion. In a study of 147 resections of cancer of the stomach at the Presbyterian Hospital, we had no cases of longevity in the invasive type, whereas in the more favorable smaller group, postoperative survivors were found living and well up to 23 years after resection.

DR J. SHELTON HORSLEY (Richmond, Va.) Doctor Allen has very effectively presented the case of cancerous change in gastric peptic ulcers. This is peculiarly appropriate because at present certain gastro-enterologists are claiming that practically never is gastric cancer developed upon peptic ulcer.

Doctor Allen has given an excellent resume of the probable changes from peptic ulcer to gastric cancer, but there are exceptions to all of those rules. I had a patient, a man age 31, who had what appeared to be a gastric peptic ulcer. The free hydrochloric

acid was 74°. He proved to have a small round cell carcinoma. He recovered from the partial gastrectomy, but eight months later had a recurrence, from which he died. Of course, this is exceptional, but the exception must be borne in mind.

Another patient, Mrs. L. E. H., age 70, had had gastric symptoms at intervals for about 15 years. A few months before entering the hospital, roentgenologic examination showed a defect in the pyloric end of the stomach. A partial gastrectomy was performed, December 10, 1928. There was a lesion on the lesser curvature about one inch from the pyloric sphincter. The ulcer was not deep but was somewhat infiltrating. Several sections showed the typical appearance of a peptic ulcer, some with regenerating epithelium and leukocytic infiltration. In one section, however, there were two adjacent acini that gave the typical histologic appearance of cancer. There were mitotic figures, a diaster, irregular nuclei, and invasion of the basement membrane. There can hardly be any disagreement as to the fact that the histologic appearance of these two acini showed cancer, and yet everywhere else that it was examined the histologic appearance was that of peptic ulcer. There appears to be no other logical explanation of this case, with the history of gastric disturbance for 15 years, than that the malignancy developed upon a peptic ulcer.

In regard to the treatment of peptic ulcer, I think in most cases a partial gastrectomy is indicated. If the ulcer is penetrating into the head of the pancreas, a type of Billroth I partial gastrectomy, which I have performed for many years, is suitable. The stomach can be divided about its middle between Pavi clamps, the distal portion lifted up, and the penetrating ulcer is shaved off with a cautery along with a thin layer of adjacent pancreatic tissue. The stump of the stomach can then be brought over and attached to the stump of the duodenum more readily than this short stump of the duodenum can be closed. There are a few recurrences after this operation, but they can be treated more satisfactorily than a recurrence after a Billroth II-type of partial gastrectomy.

DR ROSCOL R. GRAHAM (Toronto, Can.) I should like to present data showing the relation of the site of a gastric ulcer to carcinoma. In the personal cases operated upon, in which the lesion was definitely prepyloric, we found that 94 per cent were carcinoma, and only 6 per cent were benign. The group from the esophagus to the incisura showed 40 per cent malignant and 60 per cent benign. Thirty-five per cent of the latter had an organic hour-glass as evidence of their chronicity.

Singleton and Sommers, of the Roentgenologic Department of the Toronto General Hospital, studied a group in which there were 189 prepyloric gastric cancers, and during the same period they found 120 benign prepyloric ulcers. In the group of gastric cancer, ulceration was the only evidence of malignancy in 24, and in 17, or 85 per cent of those, the crater was less than 2.5 cm in diameter. This supports Doctor Allen's contention that a small ulcer may be malignant, and justifies his suggestion that, even if the person be under age 50, he will operate upon a prepyloric ulcer under 2.5 cm in diameter. There were eight cases in which carcinoma had probably developed upon a benign ulcer base. We are very anxious that all prepyloric ulcers be proven benign. This means excision, even though the ulcer be small.

MASSIVE GASTRIC HEMORRHAGE WITH SPECIAL REFERENCE TO PEPTIC ULCER*

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KNICKERBOCKER HOSPITAL, with its large metropolitan ambulance service, offers many lessons in acute emergency surgery. Among these, massive gastric hemorrhage occupies a unique place in testing the diagnostic acumen of the surgeon and the facilities of the hospital to meet a real crisis. To witness rapid exsanguination by hematemesis is a most harrowing experience to both surgeon and patient. It is a combination of concealed or silent hemorrhage with all the evidence of the shock of external hemorrhage.

Penetrating ulcer is unquestionably the most common cause of this condition. Depending upon its location, hemorrhage may be totally concealed or, regardless of its site, bleeding into the stomach may take place, followed by hematemesis.

Before proper treatment other than the emergency blood transfusion, can be instituted a differential diagnosis must be made. Usually, this can be determined by eliciting a history of gastric distress preceding the hemorrhage. Not infrequently, however, no such history can be obtained. Two cases are cited to illustrate.

A well-nourished woman, age 47, was admitted to the Knickerbocker Hospital in a state of severe shock following profuse hematemesis. No diagnostic history could be obtained as she had always been well up to the time of the hemorrhage. Postmortem examination revealed an early cirrhosis of the liver with esophageal varices. A blood clot was found in the ruptured varix.

Contrast the above case with the following. G. G., a man, age 45, was admitted for massive gastric hemorrhage. He admitted taking an excess of alcohol and gave an indefinite history of previous gastric disturbance, especially while drinking. He continued to vomit blood. A diagnosis of esophageal varix was made but autopsy revealed a punched-out gastric ulcer with a fair-sized open vessel in its center.

While it is recognized that many other conditions, to be discussed later, cause profuse hematemesis, the differential diagnosis of the two diseases illustrated by these brief case reports will be first considered. In about 10 per cent of all cases of profuse gastric hemorrhage, the history and physical examination will be inconclusive. Certain stigmata point to the diagnosis of an early cirrhosis of the liver with a bleeding esophageal varix.

(1) Spider angiomas, usually on the face, neck and back, characterized by a central point from which radiate fine hair-like branches. The central point is frequently pulsatile. These angiomas may be obliterated by com-

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pressing the "body" of the lesion with a fine pencil point. There are also "mat" nevi, slightly elevated areas of skin of a reddish or purplish color, due to uniform distention of small venules.

(2) Slight enlargement of the spleen due to chronic splenic vein obstruction.

(3) The so-called liver palms, which consist essentially of a deep reddish to purplish tinge of the thenar and hypothenar eminences of both hands.

(4) Sparse or even absent axillary and pubic hair and a distinct tendency to a female distribution is common in males. (Forty per cent of all autopsied cases at Knickerbocker Hospital.)

(5) Clubbing of the fingers.

(6) Offensive breath without any assignable local cause.

The following cases treated in the Knickerbocker Hospital presented many difficult problems in differential diagnosis.

Case 1—T. McL., age 49, fireman, gave a history of profuse gastric hemorrhage two hours before admission. History and physical examination were inconclusive. Twelve hours after admission he had an exsanguinating hemorrhage. Blood pressure 60/40. He developed severe shock. He received 1000 cc. of blood without further hemorrhage. Within 24 hours he had an upper gastro-intestinal roentgenologic examination, which was suggestive of cancer of the stomach. Later, exploratory celiotomy revealed a nonoperable adenocarcinoma which had ulcerated into a vessel of the transverse mesocolon.

Case 2—G. L., female, age 45, was admitted for severe hematemesis. Roentgenograms showed a diaphragmatic hiatus hernia with a suspicious ulcer in the herniated area. Left phrenic paralysis, with elevation of the left leaf of the diaphragm has apparently cured the condition.

Case 3—G. E., was admitted for massive hemorrhage, and gave a history of many attacks of bleeding during the past 20 years. Careful investigation, in another hospital, during these attacks failed to make a definite diagnosis of ulcer. Roentgenologic examination on admission showed redundant antral mucosa, which at times prolapsed through the pyloric ring. Operation confirmed this diagnosis.

Case 4—G. D., female, age 68, had had a pylorectomy eight months previously for an ulcer, was admitted for exsanguination. Repeated transfusions were of no avail. Autopsy revealed a leiomyosarcoma of the stomach and the anastomosed jejunum, with metastasis in the liver. Pathologic examination of the pyloric tumor removed at previous operation failed to show a malignancy.

Hemorrhage from nonmalignant tumors of the stomach has been conspicuously absent in this group.

An analysis of Allen's² statistics of 2,031 cases places the bleeding from duodenal ulcers at 41 per cent, carcinoma 20 per cent, gastric ulcer 18 per cent, marginal ulcer 3 per cent, esophageal varices 16 per cent, and unverified 2 per cent.

Frequency of Occurrence of Peptic Ulcer—During the ten-year period from 1931 to 1940, inclusive, 40,825 patients were admitted to the Knickerbocker Hospital, including 456 cases of peptic ulcer, of which 182 were admitted for gastric hemorrhage. Of 80 classified as suffering from massive gastric hemorrhage 14 died, approximately one in every 3,100, a mortality of 17.5 per cent. This accounts for the belief that massive gastric hemorrhage

is relatively uncommon and causes few deaths. In the Virginia Mason Hospital,³³ during a 20-year period, there was only one death from this cause for each 10,000 admissions to the clinic, a 15 per cent mortality. The ratio of the Knickerbocker Hospital group is much larger, due to an active ambulance service.

Pathology of Bleeding Ulcers—Bleeding from an ulcer connotes activity even though hemorrhage is the first symptomatic evidence of its presence. Erosion of the mucosa may produce moderate bleeding and even superficial ulceration of the mucosa may occasionally cause massive gastric hemorrhage although it is usually due to the erosion of a vessel of appreciable size.

The chronic penetrating type of ulcer may occur in any part of the stomach or duodenum. On the anterior and superior surfaces, a penetrating ulcer is more likely to perforate into the peritoneal cavity unless it becomes attached to a neighboring viscus. The general belief that perforating ulcers never bleed, is not true. Occasionally, erosion of a vessel in a viscus to which the ulcer has become attached and perforation at the periphery take place simultaneously. One such case was found in the Knickerbocker Hospital group and several were reported in the Questionnaire group. However, the posterior penetrating ulcer of the stomach or duodenum, with a necrotizing base in the head of the pancreas, is most provocative of massive gastric hemorrhage. In this location, a branch of the superior pancreaticoduodenal artery frequently becomes eroded. Such posterior peptic ulcers together with those on the lesser curvature, because of the proximity of the left gastric artery, account for most of the massive bleeding.

In the ulcer crater, the sclerotic artery is found terminating with an open stoma. The frequently described lateral stoma in a vessel running diagonally across the ulcer has not been noted. Found more frequently in patients above middle life, where arteriosclerosis is somewhat advanced, its mere presence in an ulcer crater, imbedded in granulation and scar tissue, is an important factor, regardless of the age of the patient, in keeping the stoma open. Chiesman¹¹ found a mortality of 74 per cent in a group of 62 patients who had bled for two or more days. Autopsy showed an open vessel in 45 of the 46 patients in this group. An eroded vessel in the crater of a chronic ulcer has frequently been found in the Knickerbocker Hospital group at operation or at autopsy. In the Questionnaire group, where autopsies or operations were reported, this was a common finding.

Symptoms—A small percentage of ulcers belongs to the "silent" type in which perforation or bleeding is the first indication of their presence. Heavy lifting while at work, recent respiratory infections, or alcoholic excesses associated with emesis are frequent exciting causes.

If massive bleeding takes place, syncope followed by hematemesis or the passage of one or more bloody stools is not uncommon. Unfortunately, the initial symptoms rarely indicate the degree and extent of the hemorrhage. Fright also may be present, especially with the first hemorrhage, and the pallor of fainting is confused with true shock. The amount of blood lost is

usually grossly exaggerated by the patient or witnesses. Blood counts are deceptive if taken before replacement of fluid, as bleeding is quantitative and not qualitative. However, an accurate estimate of the severity of the hemorrhage may be made by the rapidity of the pulse, low blood pressure, and symptoms of shock. Without a definite history of ulcer, the actual cause of the hemorrhage, whether from esophageal varices, gastric polyps, carcinoma, gastritis, redundant gastric mucosa, or simple hemorrhagic diathesis cannot be made.

General Management—All patients having gastric bleeding should be considered seriously ill and given absolute bed rest, with sufficient morphine to allay fear and restlessness.

(1) Pulse rate and blood pressure reading should be taken frequently and, if possible, by the same attendant, thus minimizing the personal error.

(2) Shock, if present or imminent, must receive appropriate treatment, ice caps to the epigastrium being definitely prohibited.

(3) As soon as possible, a Levine tube should be passed well into the stomach through the nostril for aspiration of liquid blood and lavage with saline until the stomach is free of blood clots. The removal of the blood from the stomach prevents nausea and vomiting and is of value in that a portion of the water passing into the intestines is absorbed. If, after the stomach is entirely empty, bright red blood continues to return through the tube, it is evident that hemorrhage is still active and is probably arterial, indicating immediate operation for its relief. The use of the Levine tube is, therefore, not only of therapeutic but of great diagnostic value. Soper³¹ states "I have encountered four cases in which early surgery was employed because of this appearance of the bright blood after lavage, and all four patients recovered. In each instance the surgeon located the spouting artery." As fine a record as that does great honor to the diagnostician and gives keen satisfaction to the surgeon, whose natural instinct is to ligate a bleeding vessel if he wishes to control hemorrhage.

The Levine tube may also be used for continuous or interval introduction of a liquid having acid combining power and a high caloric value.

To summarize the therapeutic value of the Levine tube:

(a) Severe straining and reverse peristalsis of the stomach is inhibited by removing the nauseating blood.

(b) Feeding is easily accomplished.

(c) The blood clot in the vessel is not mechanically removed either by vomiting, by peristalsis, or by the pangs of hunger. If lavage removes a friable clot, it is evidence of a useless clot that will not stop bleeding, such as is often seen in the throat after tonsillectomy.

(d) The ferments first removed with the blood by lavage are now combined with food and do not digest the ulcer, vessel, or clot. The Andresen⁴ diet answers this requirement perfectly.

(e) The administration of adrenalin or various coagulants through the

tube may be of value in diffuse bleeding from gastritis but obviously is of little value in the presence of an open vessel

(4) Roentgenologic examination during the bleeding period Although in the past roentgenologic examination during this period has been strictly forbidden, the acceptance of the feeding therapy for bleeding ulcer now allows such investigation of the upper gastro-intestinal tract while the hemorrhage is still active Admittedly, such an examination is incomplete Manipulation and pressure tactics are omitted These examinations have been made at Knickerbocker Hospital with satisfactory results Esophageal varices, lesions of the stomach such as ulcer or polyps, and deformity of the duodenal cap have been diagnosed The surgeon, however, must be prepared to operate should this initiate a secondary hemorrhage

(5) Typing of blood and accessible donors are essential in all cases of massive gastric hemorrhage This is particularly true in hemorrhage from an ulcer on the lesser curvature in which lethal exsanguination may rapidly develop

(6) Diet is as important to prevent recurrent ulcer in the postoperative patient as it is for healing the ulcer in the conservatively treated patient

Meulengracht,²⁴ and Andresen⁴ were in the vanguard in urging a feeding regimen as opposed to the time-honored principle of starvation for bleeding peptic ulcers Mortality statistics, as given by the advocates of these various diets, are especially difficult to understand Meulengracht reports a mortality of only 10 per cent for his group of 231 cases, while La Due,²⁰ in a recent paper, reports a mortality of 13 per cent for his group of 81 patients treated by using the Andresen diet

It is becoming generally accepted that a starvation diet, with an ice cap to the upper abdomen, should be abandoned An acceptable diet that will absorb acid and prevent action of digestive juices on the ulcer and especially on the clot in the eroded vessel, is very important However, it is very difficult to accept by ratiocination a difference in mortality of 13 per cent reported by La Due, who used the Andresen diet, with 145 per cent reported by Allen and Benedict,³ using an initial period of starvation In the Knickerbocker Hospital group treated conservatively, most of the patients were treated by the older method At present, however, the Andresen diet is being used Too few patients have been treated by the latter regimen to make a comparison

(7) Transfusions and iron medication for the resulting anemia are not necessary, as rebuilding of blood is very rapid

(8) Blood chemistry should be followed, urea nitrogen usually becoming normal soon after cessation of bleeding and replacement of circulating fluid The decreased urea clearance is due to extrarenal azotemia rather than the mere presence of blood in the gastro-intestinal tube

(9) The patient is rehabilitated by this procedure in from three to six weeks, depending upon the severity of the attack and his regenerative ability

(10) The most important of the above outlined management is that it

offers a means of selecting the lethal bleeders in the first 12- to 48-hour period. Most of them will die if treated conservatively, and should have radical treatment while still good surgical risks.

(B) *An Indication for Operation*—If continued bleeding is indicated by the syndrome of rapid pulse, drop in blood pressure, an hunger, slight delirium, reduced blood count, and hemoglobin, a transfusion sufficient to raise the blood count and hemoglobin a measurable amount should be given. If after transfusion, the red cells and hemoglobin show a marked decrease within from one to 12 hours it is certain that bleeding is taking place from an eroded vessel and immediate operation is indicated.

The value of a further decrease of blood count, not withstanding transfusion, in justifying operative interference is well illustrated in the following case.

Case Report—J. McC., male, age 34, was admitted to the Medical Service for profuse gastric hemorrhage, and was treated in the routine conservative manner. When hemoglobin reached 34 per cent, with 2,750,000 R. B. C., he received a transfusion. Forty-eight hours afterward, the hemoglobin and blood count had dropped below the previous level. He was again transfused with practically the same result, hemoglobin declining to 32 per cent, with 1,800,000 R. B. C. He was given 1,000 cc. of blood, and an emergency subtotal gastrectomy was performed under local anesthesia, plus oxygen inhalations. A posterior penetrating duodenal ulcer was resected from the head of the pancreas, the bleeding vessel found and ligated. Convalescence was entirely uneventful.

It is noteworthy that the sense of pain is so diminished in these exsanguinated patients that local anesthesia is well tolerated.

Transfusions—While transfusion of blood during an attack of massive gastric hemorrhage is now generally accepted, a small minority still believe that transfusion is contraindicated for the reason that by raising the blood pressure the clot in the bleeding vessel is dislodged, with consequent recurrence of the hemorrhage. No proof of this theoretic objection has ever been produced. On the contrary, there is much evidence to support the advantages of proper amounts of blood during the acute anemic condition.

(1) Severe grades of anemia are provocative of certain morbidities and mortalities.

(2) Production of extrarenal azotemia due to low blood pressure, resulting in a decrease in urea clearance and an increase in blood urea.

(3) Anoxemia due to poor absorption and transportation of oxygen. This may cause necrosis of tissue in vital organs, as in the brain, producing a temporary or fatal psychosis. In insufficiency of coronary circulation, even in younger individuals who have no coronary sclerosis, myocardial necrosis is produced, which is indistinguishable from myocardial infarction, yet no vessels are occluded. Such lethal lesions have been noted even in the younger group and it must, therefore, follow that it will more often occur in the older group. This, undoubtedly, is one of the explanations of the much higher death rate in the older sclerotic group, i. e., they cannot tolerate a severe grade of anemia as well as the younger nonsclerotic patients.

If transfusions are given, undiluted fresh blood containing a normal concentration of prothrombin, red cells with normal intracellular potassium, normal white cells and platelets seems to be preferable to fresh citrated blood, or banked blood, especially in patients who are near exsanguination.

The rate at which blood is given to a massive gastric hemorrhage patient has received much attention. In the Knickerbocker Hospital group most of the transfusions have been given by our hematologist Dr. Rufus Stetson.³² Amounts of 500 to 1,000 cc. have been administered by the direct method. In no case have we been able to associate a secondary hemorrhage with the amount or the rate of transfusion.

A conclusion must, therefore, be drawn that transfusion therapy should be used and that fresh blood by direct method is preferable.

Mortality from Gastro-Intestinal Hemorrhage—In few other diseases are the statistics which appear in the literature quite so difficult to evaluate. Geographic distribution, what constitutes a massive gastric hemorrhage, the ratio of gastric ulcers to duodenal ulcers, and whether cases are selected at random, such as are admitted to a metropolitan hospital from a large ambulance district, or from a clinic where careful follow-up and dietary regimens are in vogue, are factors influencing the mortality and morbidity. Hence, a variation from one to 25 per cent is found in the reported series. Hinton,¹⁷ reporting a series of 165 cases from the Fourth Division, Bellevue Hospital, has a nine per cent mortality. Chiesman¹¹ reports a 25 per cent mortality for patients having massive hemorrhage. Allen and Benedict³ report 14.5 per cent in a series of 138 cases. Goldman¹⁶ states: "The mortality of gross hemorrhage was 11.1 per cent from exsanguination alone, but rose to 15 per cent when the deaths from complications with hemorrhage were added. It should be emphasized in this connection that the additional 4.9 per cent mortality includes six patients in whom perforation ensued following the onset of hemorrhage, thus presenting two serious complications."

In 1935, Westermann³⁷ published a paper showing the appalling mortality from conservative treatment and suggested that some of these patients should be treated surgically. In the discussion of Westermann's paper, it was admitted that while he had achieved striking results, his colleagues still were inclined, in view of the operative risk, to favor conservative treatment. Since 1938, surgical treatment has had a constantly increasing number of advocates and the literature of 1939 and 1940 is replete with many articles by those who urge operative relief.

To acquire data and a cross-section surgical opinion on the subject of massive gastric hemorrhage, a questionnaire was sent to members of the New York, Western and American Surgical Associations. In all, 500 letters were sent. There were 248 replies and of these 107 furnished data. Permit me to thank the members of these associations for their courteous cooperation.

The answers indicate that 75 per cent of the surgeons strongly believe that surgery has a definite place in the treatment of massive gastric hemorrhage. The remainder are just as strongly convinced that it is entirely a medical

MASSIVE GASTRIC HEMORRHAGE

TABLE I

112 PATIENTS OPERATED UPON DURING THE ACUTE BLEEDING PERIOD

GASTRIC RESECTIONS

(BOTH SEXES)

	AGE	NUMBER	DEATHS	% MORTALITY
GASTRIC ULCERS	ABOVE 45	13	6	26
	BELOW 45	11	2	18.1
	TOTAL	24	8	23.5
DUODENAL ULCERS	ABOVE 45	55	8	14.5
	BELOW 45	23	4	17.4
	TOTAL	78	12	15.4
TOTAL ALL RESECTIONS		112	20	17.8

TABLE II

548 PATIENTS TREATED CONSERVATIVELY

CONSERVATIVE THERAPY

	SEX	AGE	NUMBER	DEATHS	% MORTALITY
GASTRIC ULCERS	M	ABOVE 45	75	22	29.3
		BELOW 45	48	9	18.7
		ALL	123	31	25.3
	F	ABOVE 45	19	5	26.3
		BELOW 45	8	0	0
		ALL	27	5	18.5
TOTAL		150	36	24	
DUODENAL ULCERS	M	ABOVE 45	164	36	21.9
		BELOW 45	179	11	6.14
		ALL	343	47	13.7
	F	ABOVE 45	35	8	22.8
		BELOW 45	20	1	5.0
		ALL	55	9	16.3
TOTAL		398	56	14.0	
TOTAL ALL ULCERS			548	92	16.7

TABLE III

HOSPITAL GROUPS TREATED CONSERVATIVELY WERE NOT COMPLETELY CLASSIFIED, AND ARE THEREFORE PLACED IN A SEPARATE GROUP

Hospital	G U *	D U †	M U ‡	Mortality Per Cent
Barnes Hospital	18	60	0	7
Bellevue—Fourth Division	17	148	0	9
Clute Howard M	4	20	6	33.3
New York Hospital	13	131	17	11
San Francisco Hospital	73	105	12	11.1
Strong Memorial Hospital	29	139	0	7.4
Toronto General Hospital	20	136	0	12
Totals	174	799	35	11.3

* Gastric ulcer

† Duodenal ulcer

‡ Marginal ulcer

problem and, if surgery is undertaken at all, it should be deferred until the patient has recovered from his exsanguination

Statistics of Conservatively Treated Cases—In the preparation of the statistical portion of this paper, 1,556 cases of peptic ulcer have been studied. Of this number, 112 were operated upon during the acute bleeding period (Table I). The remaining 1,444 were treated conservatively. This latter number is subdivided into three groups: 80 cases from the Knickerbocker Hospital (Table II), 448 from a questionnaire, and 1,008 designated as Hospital group (Table III). The Hospital group did not supply all the classifying data. A number of the conservatively treated group had interval operations, but as this is a separate problem, it is not discussed in this paper.

The mortality for the entire group of 1,556 cases is 17 per cent. The 1,008 cases in the Hospital group (Table III) have a mortality of 11.3 per cent, an apparent less rigid classification in this group. In the Knickerbocker and Questionnaire groups, massive gastric hemorrhage is interpreted as meaning a patient with 35 per cent hemoglobin or less, with a blood count of 2,000,000 red blood cells or less. Hence, moderate bleeding cases without mortality are eliminated. The 548 analyzed cases include 398 duodenal and 150 gastric ulcers, a ratio of approximately five to two. The mortality rate, however, of duodenal and gastric ulcers is reversed. It is approximately one to two, since gastric ulcer mortality is 24 per cent and duodenal mortality 14 per cent. There seems to be a general belief expressed in the literature that women withstand massive gastric hemorrhage better than men. In this analysis, there are 82 female patients with peptic ulcers, showing a mortality of 17.4 per cent as compared with 466 male patients with peptic ulcers having a mortality of 19.5 per cent (Table II).

It has long been recognized that the age of a patient is an important factor in the outcome of massive gastric hemorrhage. For purposes of analysis the age 45 was arbitrarily chosen as a dividing line.

The seriousness of bleeding in the upper age-group has been explained on the basis of arteriosclerosis. This, without doubt, is an important factor. However, in reading the histories of ulcer patients one is impressed with the length of time the average patient has had his symptoms. Furthermore, serious bleeding invariably is found in patients with chronic ulcers. In other words, serious bleeding usually takes place in old and chronic ulcers where arteritis and periarteritis is present. So, may it not be that in the older group, where the ulcer has actually existed longer, the local pathology is the deciding factor rather than the actual systemic arteriosclerosis?

Table II demonstrates that all cases of hemorrhage from peptic ulcer in those beyond age 45 is more serious than in the younger group. The mortality in 94 gastric ulcer patients above age 45 is 28.7 per cent as compared to a mortality of 20 per cent in 56 gastric ulcer patients below age 45. This is more noticeable in the duodenal ulcer group. One hundred and ninety-nine patients above age 45 had a mortality of 22 per cent as compared with 199 patients below age 45 who had only a 6 per cent mortality. The striking

difference in the mortality of these two groups does not justify too great an optimism for conservative treatment of the younger group, for it should be the responsibility of the diagnostician to recognize lethal bleeding in this group as well as in the older group

A 20 per cent mortality in gastric ulcer patients below age 45 cannot be taken lightly. A death was reported in the Questionnaire group of a boy, age 14, and autopsy showed an easily resectable ulcer. The life expectancy of patients age 14 or 18 is equal to three or four times that of patients age 50 or 60.

The tables are inserted for detailed study of the various groups since they are more expressive than word analysis.

In the Knickerbocker series there were 456 patients admitted in the ten-year period from 1931 to 1940. Of these, 173 were ruptured ulcers. One hundred and eighty-two patients were admitted for bleeding, and of the bleeding group 80 were classified as massive gastric hemorrhage, of which 14 died, a mortality of 17.5 per cent. All of these massive bleeding cases were treated conservatively except four, which were operated upon for subtotal gastrectomy, one of whom died of pneumonia on the tenth postoperative day. All deaths occurred in the group above age 45 except three, one of whom had a gastric ulcer which at autopsy showed an open vessel in a sclerosed ulcer of the antrum.

There were 57 duodenal and 23 gastric ulcers, a ratio of five to two. In the Knickerbocker group there were 16 females, with four deaths, a mortality of 25 per cent. Of the four females who died, two were duodenal ulcers above age 45 and two were gastric ulcers below age 45. There were 64 male patients, ten of whom died, a mortality of 17 per cent. Of the ten males who died, one was a duodenal ulcer below age 45, four were duodenal ulcers above age 45, four were gastric ulcers above age 45 and one was a gastric ulcer below age 45. The divisions between gastric and duodenal ulcers in the sexes were approximately the same ratio, there being four females with gastric ulcers to 12 with duodenal ulcers, and 19 males with gastric ulcers to 45 with duodenal ulcers.

The mortality rate of the entire group shows seven gastric ulcer deaths and seven duodenal ulcer deaths, a mortality of 7.6 per cent, if computed for the entire 182 bleeding cases, or a mortality of 17.5 if computed on the 80 massive gastric hemorrhage cases. This group is included with the Questionnaire group in the statistical table.

Operative Statistics—In the Knickerbocker and Questionnaire groups, 160 patients were operated upon during the bleeding period, many of them after prolonged bleeding (Table I). Of these, 112 had gastrectomies, either a Polya, a Billroth II, or some type of resection. Twenty of these patients died postoperatively, either from the operation or postoperative complications, such as pneumonia. This gives a mortality of 17.8 per cent for all types of ulcers.

TABLE IV

GROUP OPERATED UPON BY VARIOUS PROCEDURES SUCH AS LIGATION RESECTION COAGULATION *etc*

48 Patients operated upon without resection

17 Deaths a mortality of 35.4%

Admittedly most of these were less favorable surgical risks

ALPHABETICAL LIST OF CONTRIBUTORS OF CASES OF MASSIVE GASTRIC HEMORRHAGE, FROM WHICH THE DATA IN THIS PAPER IS COMPILED

Contributors	No of Cases Over Age 45	No of Cases Under Age 45	Contributors	No of Cases Over Age 45	No of Cases Under Age 45
Abell Irvin	1	1	Mason James M	2	1
Allen Arthur W	11		Masson James C	1	
Attrix Fred F		1	Mastin Edward V	3	1
Barber Robert F	8	3	Meyer Karl A	1	3
Bates Alfred K	5	3	Miller Edwin M	1	
Benjamin A E	3	4	Miller Edwin L	4	1
Best R Russell	9		Mills William M	1	
Black Carl E		1	Mixter Charles E	10	1
Bonn Harry K		1	Moore Edward C	1	2
Burdick Carl G and Hinton J Wm	Bellevue Hospital—Fourth Division 165 cases peptic ulcer reported		Moore Robert M	3	3
			Morrison Wayland A	3	
Carson William J		4	Morton Paul C	1	1
Cave Henry W		1	Morton Lewis B		1
Clute Howard M	30 cases reported in Hospital group		Motzel Albert J		1
			Oughterson Ashley W and Harvey Samuel C	3	1
Cole Warren H		1	Packard George B Jr	1	6
Cottam Gilbert	1	1	Patterson Russell H		2
Dixon Claude F	1		Percy Nelson M	21	16
Donovan Edward J	4	2	Peterson F R	7	1
Fudley Guilford S	1	4	Powell Lester D	1	2
Dyas Frederick G	1		Primrose William A	1	
Eggers Carl	1	2	Reichert Frederick L	1	1
Eloesser Leo and Klein Russell	San Francisco Hospital 250 cases peptic ulcer reported		Wiggs Theodore F	4	2
			Russell Thomas H	2	1
Evans John L	4	1	Sanders Robert L	4	1
Fahrni Gordon S		4	Sauer Paul K	2	4
Fairchild Fred R	1	1	Schmidt Edwin R	9	5
Fawcett George G	2	1	Schwyzzer Arnold	2	1
Foster John M Jr	1		Scott W J Merle		
Foss Harold L	9	7		Strong Memorial Hospital 168 cases reported	
Gallie William E		1	Seeger Stanley J	1	
Garlock John H	2	3	Smith Joseph F	1	
Gillespie M G	12	10	Smith Morris K	3	
Grace Roderick V		1	Smithwick Reginald H	1	1
Graham Evarts A and Kelly Robert	Barnes Hospital 78 cases reported		Smyth Calvin M Jr	3	2
Graham Henry F	8	10	Stone Harvey E	1	1
Graham Roscoe R	Toronto General Hospital 156 cases reported		Sturgeon Charles T	2	6
			Summey Thomas J	2	1
Hart J Deryl	3	6	Taylor Alfred S	1	
Hegner Casper F	2	4	Toland Clarence G	2	3
Hertzler Arthur E	1		Truesdale Philemon E	10	9
Heuer George J and Holman Cranston W	New York Hospital 161 cases reported		Twyman Elmer D	4	
			Vaughan George T	1	
Heyd Charles G		1	Wallace Hilen K	4	2
Holden William B	2		Westermann John J	5	3
Horsley J Shelton	5	2	Williams Carrington	7	2
Hunt Claude J	2	1	Wise Walter D	4	4
Hunt Verne C	9	3	Wright Arthur W and Barber W Howard		
Ide Arthur W	2	1		Reported six cases having gastro-enterostomies who subsequently had massive gastric hemorrhage	
Jackson Arnold S	6	4	Zinninger Max M	6	3
Joyce Thomas M	4		No name	1	1
Larson E Eric	1		No name	1	
Lee Walter E	11	7	No name	1	
Lehman Edwin P	2	1	No name		1
Long Le Roy D	8	7	No name	1	5
McDonald A L	1		No name	1	3
MacFee William F	1				
Maes Urban	Louisiana State University 33 cases reported				

There were 23 gastric ulcer patients above age 45, with six deaths, a mortality of 26 per cent. This compares favorably with the conservatively treated gastric ulcer cases. Ninety-four patients in the same age-group had 27 deaths, a mortality of 28.7 per cent.

In the group of duodenal ulcers above age 45, there were 55 operated upon, with eight deaths, a mortality of 14.5 per cent, as against the conservatively treated group of 199 patients with 44 deaths, a mortality of 22 per cent. Had these patients been operated upon in the 24- to 48-hour period, it is reasonable to assume the mortality would have been nearer that of interval gastrectomies, or near that of Finsterer¹⁵ who performed 71 gastrectomies upon bleeding ulcer patients, with a mortality of 4.2 per cent.

The use of chemotherapy, given either preoperatively or as a massive dose intraperitoneally at the end of the operation, may still further reduce this mortality, especially since pneumonia seems to be a complication causing many of the deaths.

Forty-eight patients were treated by various operative procedures: gastroenterostomies, pyloroplasties with excision of the ulcer, enterostomies or gastrostomies with ligation of the bleeding vessel or coagulation of the bleeding point. It is fair to presume that these patients were less favorable surgical risks, otherwise gastrectomies would have been undertaken. Of these 48 patients 17 died, a mortality of 35.4 per cent (Table IV).

CONCLUSIONS

Analysis of this data justifies the following conclusions:

(1) Gastrectomy is the operation of choice, both for control of hemorrhage and for an ultimate cure. Bleeding following gastrectomy in surviving patients was not reported.

(2) Gastrectomy is often more difficult to accomplish in cases of duodenal than in cases of gastric ulcer.

(3) Local excision of a gastric ulcer combined with gastro-enterostomy apparently gives a satisfactory result.

(4) If the ligation of a vessel or plication of the ulcer only is accomplished, nonabsorbable suture material should be used. However, bleeding has recurred following this procedure.

(5) Gastro-enterostomy *per se* is of no value to stop immediate bleeding or to prevent recurrence.

(6) Vitamins, particularly B and C, given preferably by hypodermic in the postoperative period, will aid materially in an uneventful convalescence.

(7) Early operation before repeated exsanguination occurs, is essential for a lowered mortality.

SUMMARIES OF CASES OF SPECIAL INTEREST

Cases Reported in the Questionnaire Group

Dr. William E. Gallie. *Recurrent Hemorrhage*

Male, age 43, with a five year history of gastric ulcer. Admitted to hospital with hematemesis and hemoglobin 80 per cent. Treated conservatively. Nine days later, a second profuse hemorrhage.

occurred after which the hemoglobin was 43 per cent. In spite of transfusions the hemoglobin fell to 32 per cent. A gastrectomy was then performed. Recovery uncomplicated and the patient is now symptom free.

Dr James C Masson *Lethal Hemorrhage without Demonstrable Lesion*

A patient operated upon for repair of a postoperative interstitial hernia. At the same time a vaginal hysterectomy for uterine prolapse and cystocele and a perineorrhaphy for lacerated perineum was done. She had an uneventful convalescence. On the eleventh postoperative day she passed a tarry stool. In spite of treatment she died in a comparatively short time. Autopsy revealed the stomach to contain 1500 cc and the intestine 500 cc of blood but the source of bleeding could not be found.

Dr E Eric Larson *Cauterization for Bleeding*

(1) Male age 58 was admitted for severe indigestion. Fifteen days later he had a very severe gastric hemorrhage. Operation: Duodenotomy with cauterization of the pancreatic base of the ulcer. Pyloric occlusion with gastroenterostomy was then performed. Patient recovered and has been well for the past two years. Roentgenograms show pylorus and gastroenterostomy, stomach both functioning.

(2) *Small Bleeding Ulcer Difficult to Find*

Male age 38 died from massive gastric hemorrhage. When the stomach and duodenum were opened at autopsy no bleeding point could be seen. Upon stroking the posterior wall with the hand a fountain like spray emitted through a pin head sized hole. Could the surgeon have found it?

Dr Thomas H Russell *The Young Die Too*

Boy age 14 was admitted to the hospital for massive gastric hemorrhage. He was treated conservatively. Autopsy revealed a small ulcer on the anterior wall of the duodenum, which would have been easily resectable.

Dr James M Mason *Recurrence of Bleeding*

Male age 64 was admitted for massive gastric hemorrhage. He was alcoholic and had cardio-vascular renal disease. Hemoglobin on admission was 35 per cent, RBC 1,950,000. He was treated conservatively followed by recovery. Readmitted nine months later for massive gastric hemorrhage. Hemoglobin 28 per cent, RBC 2,000,000. Bleeding continued in spite of treatment. Autopsy revealed a duodenal ulcer with erosion of gastroduodenal artery.

Dr Roderick V Grace *Bleeding Recurrent after Ligation*

Male age 35 was admitted for massive gastric hemorrhage. Duodenotomy was performed and a posterior duodenal ulcer with a vessel in the center was located. A gastrectomy was not feasible so the bleeding artery was ligated with chromic ligature. The ulcer was too fixed to admit its being plicated. Bleeding stopped but on the fifth postoperative day the patient died of an apparent recurrent hemorrhage.

Dr Albert J Motzel *Death from Pneumonia*

Male, age 24 was admitted for massive gastric hemorrhage. He passed red blood by rectum, blood pressure not obtainable, pulse fast. After a 1000 cc blood transfusion his pressure was 70/50. In three days another severe hemorrhage occurred, pulse 120, RBC 1,700,000. He received a large transfusion, with temporary recovery but continued to bleed. Duodenotomy under local anesthesia on the seventh day disclosed a posterior duodenal ulcer with bleeding artery which was ligated with silk. Patient improved and four days later RBC 4,240,000, 12.3 Gm hemoglobin. On the fifth postoperative day he developed pneumonia and in spite of chemotherapy succumbed on the twenty-ninth postoperative day.

Dr Reginald H Smithwick *Extent of Operation Possible*

Male age 30 had had repeated hemorrhages during a period of three weeks. RBC 1,500,000. At operation an ulcer was found on the lesser curvature, posterior wall involving the gastric artery. The crater was 3 cm in diameter and the ulcer proved to be cancerous. Practically a total gastrectomy was performed with recovery.

Dr Irvin Abell *Perforation and Bleeding Ulcer*

Male age 42. Past history of typhoid. Had recurrent attacks of excruciating pain in abdomen over a period of 12 years. On admission stools had been tarry for past 24 hours. He was given two blood transfusions totaling 915 cc. Bleeding continued and hemoglobin reached 30 per cent, RBC 1,860,000. After the transfusions a celiotomy demonstrated a perforated gastric ulcer partially concealed by the liver, colon and omentum. Polya type of gastrectomy was performed, also appendectomy resulting in a cure.

Dr Edwin M Miller *Massive Transfusion*

Male age 64 was admitted for massive gastric hemorrhage. At noon he was in *extremis*. A continuous blood transfusion was then started and at four o'clock his condition was thought to be operable. The stomach was dilated and solidly filled with a massive blood clot which could only be

removed by scooping it out by hand. After removal of the clot, it was possible to see a pumping gastric artery in the center of a saddling ulcer on the lesser curvature. A Billroth II resection, with an anterior gastroenterostomy and an enteroenterostomy were performed. One year postoperative the patient is in excellent health.

Dr John M Foster Jr *Successful E-cen After Long Delay*

Male, age 48 with chronic ulcer. Admitted after four days of profuse bleeding. RBC 1,250,000. Improved with conservative treatment, but on ninth day after admission he again had moderate hematemesis. On the eighteenth and nineteenth days, he vomited copious amounts of blood. A posterior duodenal ulcer was found, with an artery that spurted ten inches. The ulcer could not be removed on account of the induration. A posterior Polya, with exclusion of the ulcer was performed. Upon being brought to the operating room both arms were placed on arm boards and with four available donors we transfused him in both arms. The amount of blood received during surgery was about 1,200 cc. He left the table with a much better color and a distinct slowing of the pulse. Convalescence was complicated by pneumonia. To date he is in excellent condition without symptoms.

Dr William F MacFee *Successful Subtotal Gastrectomy*

Male, age 61 had had intermittent exanguinating hemorrhages for three weeks of such severity and frequency that operation became imperative. A subtotal gastrectomy was therefore, performed with cure of the patient.

Dr Claude F Dixon *Reactivation with Bleeding of an Apparently Healed Duodenal Ulcer*

A gastroenterostomy gave relief for 16½ years. He was readmitted for a large tumor in his upper abdomen suspected of being a carcinoma. Exploration revealed a gastrojejunalcolic fistula. Jejunostomy was performed at this operation for feeding purpose. The mass rapidly disappeared. The abdomen was reopened four weeks later and as the duodenal ulcer had practically disappeared the gastroenterostomy was disconnected, the marginal ulcer excised and normal continuity reestablished. A double-barrel colostomy was then made at the site of the colon fistula. Progress was excellent for three weeks when a terrific hemorrhage occurred. He was given 16 transfusions, two being of 1,500 cc, three of 1,000 cc, and 11 of 500 cc. He was never transfused except as a last resort. Autopsy revealed a reactivation of the duodenal ulcer with erosion of the pancreaticoduodenal artery.

Dr Walter D Wise *Bleeding after Exclusion Operation*

Female, age 34 suffering from recurrent hemorrhages. She was explored and such an extensive duodenal ulcer was found that resection was considered impossible. A gastroenterostomy was performed. She subsequently bled again. A second exploratory was done at which time resection was again considered too formidable, so a Divine exclusion operation was performed. This gave the patient relief for about five years. She recently had another attack of bleeding.

Dr Guilford S Dudley *(Second Surgical Division—Belleue) Duodenal Fistula*

Male, age 74 was admitted with perforated prepyloric ulcer for which he was successfully operated upon. On the twenty-second postoperative day, he had a severe gastric hemorrhage followed by shock. Supportive treatment with 500 cc transfusion caused improvement. In 24 hours he had a second severe hemorrhage with marked shock, blood pressure 96/66, pulse 130. Continuous transfusion and operation followed. There was a large posterior duodenal ulcer penetrating into the pancreas, with an open vessel. Subtotal gastrectomy with resection of the ulcer and ligation of the bleeding vessel was accomplished. Difficulty was encountered in closure of the duodenal stump, cigarette drain down to the duodenal stump and wound closed. Duodenal fistula developed on fourth postoperative day with drainage of blood and bile. Patient developed pneumonia and died on thirteenth postoperative day.

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SURGERY IN PEPTIC ULCERATION OF STOMACH AND DUODENUM IN INFANTS AND CHILDREN*

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BECAUSE of the general impression that peptic ulceration of the stomach and duodenum is excessively rare in infants and children, there is a tendency to neglect this lesion in young patients. For this reason, it seems to us of interest to present evidence which, though largely indirect, indicates that the disease is not very uncommon.

Several internists and roentgenologists (*e.g.*, Nisbet, 1911, Michaelsson, 1925, Dickey, 1926, Potter, 1930, Jankelson, 1932, Reuben, 1934, Hirsch, 1935, Prévôt, 1935, Blechmann, Gutmann and Nemours-Auguste, 1932) have published two or more cases in which the diagnosis of peptic ulcer was adequately established on clinical grounds, and others (Weithember, 1882, Adler, 1907, Loeber, 1929, Herz, 1930, Oldfield, 1932, Bermond, 1933, Moore, 1934, Gillespie and Gianturco, 1935, Menna, 1937, Cathala, 1938) have reported individual examples in this category. Many of these authors voice the opinion that the disease is not rare but frequently overlooked. Altogether, a considerable number of ulcers, about 200 or 300 in the world literature, have been demonstrated at autopsy,[†] and undoubtedly many have existed undiagnosed in patients who have recovered or who have died without postmortem examination.

By careful search, we have gathered what we believe to be an almost complete collection of the cases reported in which operations have been performed for peptic ulcers in infants and children. The cases number 119, and include one of our own. The diagnoses, we think, though based on clinical features

* This paper is not concerned with peptic ulceration of the esophagus or of Meckel's diverticulum. For those who are interested in these subjects, the articles by Diamantopoulos (1926), and Black and Benjamin (1936) should be consulted.

† Through the kindness of Dr. B. Earl Clarke, pathologist at the Rhode Island Hospital, we record, here, a previously unpublished case of an acute ulcer of the posterior wall of the duodenum, 3 mm. in diameter, observed at autopsy in a male, aged two months. The infant was well until two or three days before death. It then refused food and whined as if in pain. There was no vomiting, and blood was not noticed in the stools. Except for a moderately enlarged heart with a patent foramen ovale and a wide interventricular defect, nothing else abnormal was observed at the postmortem examination. A blood culture was not made.

of gross observations at operation in some of the patients in whom gastroenterostomy alone was performed, can scarcely be questioned. We have also accumulated representative reports of 124 cases in which no operation was undertaken. In most of these instances, the diagnoses were established at autopsy, and in the others the clinical features, often substantiated by characteristic roentgenologic findings, were unmistakable.

An analysis of our collected cases shows that ulcers in the newborn, by which we mean infants in whom the symptoms become outstanding within the first two weeks of life, have special characteristics: (1) The great majority, at least of ulcers that are recognized, bleed seriously, or perforate, or do both (Table I), (2) in many the onset is precipitous without recognizable premonitory symptoms or signs, (3) except in a few cases, neither clinically nor at autopsy, is there evidence of intracranial injury, or localized or generalized sepsis, (4) with few exceptions the lesions are acute, without cellular reaction or bacterial invasion, (5) because of the sudden, acute, fulminating symptoms, very few of these newborn patients are operated upon, (6) duodenal ulcers outnumber the gastric in a ratio of 2:1 (Table II), and (7) males outnumber females, but not strikingly so (Table III).^{*}

Peptic ulcers have been shown to occur even *in utero* (Lee and Wells, 1923).

TABLE I
TYPES OF ULCER REPORTED IN VARIOUS AGE-GROUPS

	Stenosing	Perforated	Bleeding	Persistently Painful etc	Totals
Newborn (0-14 days)	1	18	22	1	42
15 days-1 year	8	15	25	6	54
2-6	2	3	10	5	20
7-11	18	15	8	16	57
12-15	31	26	3	12	72
Totals	60	77	68	40	245

- Note that (1) At least among the cases which have been recognized ulcers in the newborn and in the early months of life characteristically either bleed seriously or perforate or do both.
 (2) The number of cases of all types which are recognized is small in children between two and six years of age.
 (3) Among the recognized cases the incidence of pyloric stenosis and perforation increases during the later years of childhood while the occurrence of serious hemorrhage decreases.
 (4) After the eighth year there are a considerable number of patients with uncontrollable abdominal symptoms especially pain.

During the first 24 months of life, beyond the newborn period, the number of infants with ulcer diminishes. The nature of the disease also changes, as follows: (1) Although again the great majority of ulcers bleed grossly, or perforate (Table I), there are often premonitory symptoms such as refusal of feedings, evident abdominal pain, vomiting, occasional streaking of blood in the vomitus and melena, sometimes occurring over a period of weeks or

* Kennedy (1926), and others, believe that most cases of melena neonatorum are due to ulcers, and that many of them heal. He states (1924) that acute ulcers are often overlooked at autopsy, and that, frequently, they are quite invisible in a fresh specimen although they may be seen easily if the specimen is examined after a few hours of fixation.

months before the onset of graver symptoms, (2) persistent pylorospasm or inflammatory or cicatricial pyloric stenosis is seen occasionally, (3) many of the patients are septic and marasmic, and the ulcers when seen at autopsy present, as a rule, an acute, subacute or chronic inflammatory base in which are seen numerous bacteria, (4) because of poor general condition very few of these patients are operated upon, (5) in an undetermined number, the symptoms recede and health is regained, (6) in this group the duodenal and pyloric ulcers outnumber the gastric in a ratio of more than 5 : 1 (Table II), and (7) males outnumber females (Table III)

TABLE II
RATIO OF DUODENAL AND PYLORIC TO GASTRIC ULCERS IN VARIOUS AGE GROUPS

	Duodenal and Pyloric	Gastric	Total
Newborn (0-14 days)	26 (2)*	12 (1)	38
15 days-1 year	43 (5)	8 (1)	51
2-6	16	6	22
7-11	44	16	60
12-15	55	17	72
Totals	184 (3)	59 (1)	243

* Ratios are in parentheses

Note that (1) The ratio of duodenal and pyloric to gastric ulcers is approximately 2 : 1 in the newborn

(2) This ratio is about 3 : 1 for the entire group

Between the ages of two and six years, the recognized examples of the disorder are very few (Table III). Among 243 cases, only 22 occurred within this period. This contrasts strongly with 89 recorded for the first 24 months of life, 60, for ages between seven and 11 years, and 72 for ages between 12 and 15. Among the examples reported, chronicity, hemorrhage, perforation and stenosis are outstanding features and, except in the children with burns, foci of infection are observed only rarely.

TABLE III
AGE AND SEX DISTRIBUTION AMONG 243 CASES OF
DUODENAL AND GASTRIC ULCER

	Male	Female	Sex Not Stated	Total
Newborn (0-14 days)	15	11	12	38
15 days-1 year	22	15	14	51
2-6	11	9	2	22
7-11	35	22	3	60
12-15	43	23	6	72
Totals	126	80	37	243

Note that in all age groups males outnumber females but not strikingly so. The ratio of males to females for the total number is approximately 1.5 : 1.

As age advances beyond the seventh year, there is a rise in the number of cases recognized, with special accentuation of the symptoms of pyloric stenosis and perforation (Table I). Hemorrhage recedes into the background. A few of the children require surgical treatment because of persistent, uncontrollable indigestion.

Over 70 per cent of the patients reported between the ages of seven and 15 were operated upon. On this basis there must be a large number of unrecognized or unreported cases of acute or subacute ulcer at this time of life, for it is scarcely possible that such a high proportion of the ulcers of childhood should lead to complications which require surgical intervention. It seems probable that acute and subacute ulcers masquerade under diagnoses such as chronic appendicitis, intestinal tuberculosis, mesenteric lymphadenitis, vermiculosis, allergic indigestion, or neurosis.

Among the cases reported in this age-group (seven to 15), the symptoms have often been present intermittently or continuously over a period of months or years. Chvostek (1882) noted a male, age 18, who had had indigestion since age four. Autopsy showed two large, round gastric ulcers, one at the cardia and one at the pylorus, the latter of which had caused pyloric obstruction. Paimentier and Lasnier (1908) told of a female, age 20, whose symptoms of ulcer had been present since infancy, she was improved on medical treatment. Pepper (1899) observed an autopsy on a patient, age 20, whose epigastric symptoms dated back to early childhood and in whom death was due to cicatricial pyloric stenosis. Among patients who were operated upon after the age of 15, and who, thus, were not included in our collection, Ettman (1936) recorded the story of a girl, age 16, whose symptoms for the preceding 18 months were characteristic of ulcer and who then perforated the duodenum, Schaliy (1923-1924) reported upon a female, age 18, with recurrent epigastric distress since the age of 12, and high gastric acidity, who at operation revealed a callous ulcer of the duodenum, and Bignami (1939) described a girl, age 17, who had been treated for abdominal distress since the age of 11, and whose chronic duodenal ulcer was relieved by gastro-enterostomy. Von Cackovic (1912) and Proctor (1925) noted that in a considerable number of cases of ulcer in adults the symptoms date back to childhood. Several authors (Kalk, 1928, Rogers, 1928, Hirsch, 1935, Meltzer and Graf, 1936, and Bloch and Serby, 1937) stress the frequency of a familial history of ulcer in affected children.

Surgical Considerations—Because of advances made in management during the preoperative, operative and postoperative periods, operations upon children, generally speaking, are safer than they were formerly. No rule of thumb can be made in regard to infants and children who present gross gastro-intestinal hemorrhage, or in those in whom septic or marasmic conditions such as malnutrition, furunculosis, otitis media and burns, complicate the picture, but for otherwise healthy children with chronic hemorrhage, perforation, pyloric occlusion, or those in whom pain persists after adequate medical treatment, operation may be said to be indicated.

Our interest in surgery of peptic ulcer in infancy and childhood was aroused by the following case:

Case Report—Perforated Duodenal Ulcer—Sutured 34½ hours after birth. Recovery. F. W. F., colored, normal appearing, full-term, male infant, weighing seven

pounds and one ounce, was born in the Louisville City Hospital February 19, 1934, at 11 03 A M

The mother, age 25, had given birth to four full-term infants in the hospital previously. The third one had died one week after a Ramstedt operation for pyloric stenosis, there was no autopsy. There had been one miscarriage at the third month, but the history did not suggest tuberculosis or syphilis, and the mother's blood Wassermann reaction had been negative on all admissions. When seen in the Prenatal Clinic during the eighth month the blood Wassermann reaction was again negative. Labor began at 2 A M, February 19, 1934, and she was admitted to the hospital four hours later. The membranes ruptured at 10 45 A M. During the second stage, which lasted 18 minutes, chloroform was administered in small amounts, and the birth was completed spontaneously in the left occiput anterior position.

There was no asphyxia and the infant cried immediately. He was put to the breast at 6 P M and at 10 P M, and took 35 cc of water during the first 12 hours. On the day of birth he had one normal meconium stool and voided once. On the next day he was placed on the breast every four hours and allowed water in 15 to 20 cc amounts between feedings. Another meconium stool was passed and he voided twice. When he was fed at 2 P M, 27 hours after birth, nothing abnormal was noted, but he cried a great deal shortly afterward, and at 4 30 P M, 29½ hours after birth, the nurse observed that the scrotum was swollen and that the abdomen was distended. He had not vomited. The rectal temperature was 99.8° F. He was given a colonic irrigation, upon which a pasty, brown stool and a little gas were expelled.

When seen at 6 30 P M, the abdomen was moderately distended, and the scrotum was ballooned so that the skin seemed stretched to the thinness of paper. The scrotal sac was symmetrical, transilluminated readily, and was tympanic on percussion. The scrotum could be reduced in size by compression, but on release it refilled and, if at the same time pressure was exerted on the abdomen, the scrotum would distend with a swishing sound. Rectal examination showed nothing abnormal.

Roentgenograms were made with the infant upright, and again in an inverted position. They showed a very large amount of free air in the peritoneal cavity and in hernial sacs, which extended into the scrotum. The findings were diagnostic of a perforation in the gastro-intestinal tract, although the exact nature of the lesion was not suspected preoperatively.

Abdominal exploration was performed under chloroform anesthesia at 9 30 P M, 34½ hours after birth. This procedure was carried out by Dr. Jacob M. Mayer, then resident surgeon. On opening the peritoneal cavity, free gas and a small amount of serosanguineous fluid were observed. There was moderate hyperemia of the serous surfaces and, here and there, loops of small bowel were bound together by fresh fibrin. The tip of a finger could be introduced into both sides of the scrotum, but no bowel or omentum was present in either hernial sac. Investigation of the upper abdomen revealed an exudate in the region of the gallbladder and duodenum, where all the structures were matted together. When the fresh adhesions were separated, a perforation was found on the anterosuperior surface of the duodenum, immediately distal to the pyloric vein. A moderate amount of bile and mucus exuded from it. The perforation was oval in shape and about 3 Mm in greatest diameter. There was no induration or edema of its borders and the opening appeared as though a bite had been taken out of the normal duodenum by a sharp instrument. The defect was closed transversely with a row of fine, interrupted chromic catgut sutures and was reinforced by a tier of "A" silk sutures over which was drawn a portion of the gastrocolic omentum. The abdomen was closed securely in layers without drainage. In applying the dressing, the wound was isolated from the umbilicus.

The infant was returned to the ward in excellent condition and was given 80 cc of 10 per cent dextrose solution intravenously and 350 cc of isotonic sodium chloride

subcutaneously During the following 11 hours he vomited small amounts of brownish fluid on three occasions

At 11 A M the next morning, 15 mg of phenobarbital in a small amount of water were administered by mouth, for restlessness After 3 P M, he took water by mouth in 15 cc amounts at one and one-half hour intervals At 6 15 P M, he vomited again and gastric lavage evacuated a moderate amount of brownish fluid The abdomen was not distended and the rectal temperature had not risen above 99.8° F He was given 100 cc of 10 per cent dextrose intravenously and 125 cc of Hartmann's Ringer-lactate solution subcutaneously By this time cultures of the free peritoneal fluid, taken at the time of operation, showed no growth

On February 22, the second postoperative day, the rectal temperature rose at 8 A M to 102.2° F At 9 A M, he was given 10 cc of breast milk with 10 cc of water, at noon and at 3 P M he was fed 15 cc of breast milk with 10 cc of water and at 6 P M and 10 P M, 20 cc of breast milk with 10 cc of water Water was also given, 30 cc at a time, during the day, half-way between feedings, and 125 cc of Hartmann's solution were administered subcutaneously

On February 23, the third postoperative day, he was fed, as on the last previous occasions, at 2 A M, and 6 A M, and was then put to the breast every three hours, each feeding was supplemented by 30 cc of breast milk The rectal temperature on this day remained below 99.6° F, and the abdomen was soft

On February 24, the fourth postoperative day, the temperature was normal and remained so throughout the rest of the stay in the hospital He took the breast fairly well, although it was necessary to continue the supplementary feedings The weight, which had dropped seven ounces on the second postoperative day, again approached the birth weight On the ninth postoperative day he weighed eight pounds, but gradually lost again to seven pounds and two ounces on March 10, then gained gradually The wound healed cleanly There was no apparent infection at the umbilicus at any time

On March 9, the seventeenth postoperative day, a gastro-intestinal examination showed 25 per cent retention of barium in the stomach at six hours, there was a slight residue in the stomach after 24 hours The infant was discharged in excellent condition March 17, 1934, 26 days after operation His weight on this date was seven pounds and nine ounces

The barium meal was repeated on March 31, 40 days after operation Sixty per cent was found in the stomach at the end of six hours Five hours later, there was still a large amount of barium in the stomach, but some of it was scattered through the intestinal tract At 24 hours, the infant had not vomited, and the stomach and most of the bowel were empty

The patient was readmitted for observation November 2, 1934, at the age of eight and one-half months According to the mother he had been well since discharge He had never vomited and the bowels had moved without medication He had eaten cereals and vegetables in addition to breast milk, orange juice and cod liver oil He was found to be well-developed, and weighed 17 pounds The abdominal wound was solidly healed He had an umbilical hernia Both inguinal rings were enlarged but definite herniae could not be demonstrated The testicles were palpable in their normal positions On November 5, the gastro-intestinal examination was repeated At the end of six hours there was slight retention of barium, and four hours later the stomach was empty On November 11, a gastric analysis, using for stimulation 60 cc of 7 per cent alcohol with histamine added, gave clear, mucoid specimens which contained no blood, the fasting specimen showed free hydrochloric acid 32, total 58, at one-half hour, free 18 and total 24, at one hour, free five and total nine

On April 30, 1935, 14 months after operation, the child was returned for further observation He had been well, and his development had proceeded satisfactorily On May 3, a barium meal revealed the stomach and duodenum to be normal in size, shape, position and function Barium passed freely from the pyloric antrum into the duodenum and

there was no six-hour residue. The gastric analysis was repeated, this time using 50 cc of 7 per cent alcohol and 0.09 cc of 1:1,000 histamine solution. No free hydrochloric acid was found in any of the specimens, the total acidity in the fasting contents was 18, at one-half hour 50, and at one hour 45. Possibly, it is of significance that on the day this determination was made, the rectal temperature was 101.2° F, two days later he was transferred to the isolation ward with a well-developed case of measles. Recovery was complicated by acute catarrhal otitis media.

The child was studied again in February, 1940, at the age of six. He was in good health. Gastro-intestinal examination showed the esophagus and stomach normal and empty at six hours. There was a smooth outpouching from the duodenal bulb which gave the appearance of a small diverticulum. At 24 hours, the entire tract was empty of barium except for the lower colon. Gastric analysis showed for the fasting specimen free hydrochloric acid two, total 150, one hour after 60 cc of 7 per cent alcohol, free 20, total 130.

TABLE IV
SITUATION OF ULCERS AND INDICATIONS FOR OPERATION

	Pyloric Obstruction	Perforation	Hemorrhage	Persistent Pain <i>etc</i>	Totals
Stomach	7	21	1	1	30
Pylorus or duodenum	42	21	10	10	83
Pylorus and duodenum	4				4
Stomach and duodenum		1			1
Accessory pouch of anomalous stomach			1		1
Totals	53	43	12	11	119

Note that (1) The pyloric and duodenal lesions constitute 72 per cent of those operated upon.

(2) The indications for operation are for the most part pyloric obstruction, perforation of the duodenum or stomach, hemorrhage from the duodenum or persistent pain due to a pyloric or duodenal ulcer.

Among the 119 cases of peptic ulcer of the stomach or duodenum operated upon between the ages of 34½ hours and 15 years, 53 were for pyloric stenosis, 43 for perforation, 12 for hemorrhage and 11 for uncontrollable symptoms (Table IV). The stomach was involved in 30 cases, the pylorus or duodenum in 83, while in five other cases there were multiple lesions involving more than one part, and in one there was an ulcer in an accessory pouch of an anomalous stomach.

TABLE V
INDICATIONS FOR OPERATION AND NUMBER OF PATIENTS OPERATED UPON IN VARIOUS AGE GROUPS

	Pyloric Obstruction	Perforation	Hemorrhage	Persistent Pain <i>etc</i>	Number of Patients Operated Upon
Newborn (0-14 days)	1	5			6
15 days-1 year	3	3	3		9
2-6	1	3	4		8
7-11	18	7	2	4	31
12-15	30	25	3	7	65
Totals	53	43	12	11	119

Note that (1) Most of the operations have been upon older children.

(2) The largest number of procedures have been carried out for pyloric obstruction and for perforation, a smaller number for hemorrhage and persistent symptoms.

The indications for operation and the number of patients operated upon in the various age-groups are shown in Table V. In the very young, the

PEPTIC ULCER IN CHILDHOOD

indications were Persistent pylorospasm, pyloric stenosis, perforation or hemorrhage, in the small group between the ages of two and six years, hemorrhage or perforation, and in the larger groups between seven and 15 years, predominantly cicatricial or inflammatory pyloric stenosis, acute perforation or, in a few, uncontrollable pain. Most of the operations were performed in later childhood.

TABLE VI
TYPES OF OPERATION, AND MORTALITY RATES*

	Closure of Perforation	Pyloroplasty or Gastro- enterostomy	Resection	Totals	Mortality Rate (Per Cent)
Newborn (0-14 days)	5 (4)			5 (4)	80.0
15 days-1 year	2 (1)	2 (1)	1 (1)	5 (3)	60.0
2-6	1	2	1	4	0.0
7-11	5 (1)	21 (1)	4	30 (2)	6.7
12-15	24† (2)	30	11 (1)	65 (3)	4.6
Totals	37 (8)	55 (2)	17 (2)	109 (12)	11.0

Parentheses indicate deaths.

Note that the mortality rate in the very young has been high while the rate in the older children has been quite low.

* The following cases are not included in this table:

Sanjck, Weber, Becker, result not stated.

Michaëlsson, gastro-enterostomy, resection elsewhere at age 21 for jejunal ulcer, result not stated.

Michaëlsson, gastro-enterostomy, second operation at age 17 for jejunal ulcer, died.

Bufe, John, appendicectomies in patients with bleeding ulcers, died.

Lee and Wells, lysis of adhesions in newborn infant with perforating gastric ulcer, died.

Berglund, exploratory celiotomy in an infant with bleeding duodenal ulcer, died.

Phélip and Fey, operative perforation of small bowel in infant with perforated gastric ulcer, died.

Shore, exploratory celiotomy in infant with perforated gastric ulcer, died during operation.

von Mönitz, exploratory celiotomy in child with perforated duodenal ulcer and peritoneal abscess, died.

Bechtold, drainage of abdomen, only, in child with perforated gastric ulcer, died.

Peutz, exploratory celiotomy for bleeding duodenal ulcer, recovered.

† The case of Andersen is included in this table both under closure of perforation and under gastro-enterostomy and the case of Angel and Angel and two of Deuticke are included both under closure of perforation and under resection. In each case there was a long interval between the first and second operations.

The procedures (Table VI) are grouped under the headings Closure of perforation, gastro-enterostomy (including pyloroplasty), and resection. Although closure of a perforation was carried out in five newborn infants, only our own recovered. The next youngest survivor was a male, age three months, reported by Selinger (1930)—with a recent perforation of the stomach which had sealed over. Downes (1923) successfully sutured an acute perforation of the duodenum in a child, age three. Between the ages of seven and 11 years, five perforations were closed with only one death—in a very ill child, age nine, whose perforation occurred nine days before operation. In the age-group between 12 and 15, 24 perforations were closed with only two deaths, one in a child, age 14, who was operated upon after a delay of 21 hours, and the other, in a boy, age 15, who died 17 days after operation because of an apparently unrelated intestinal obstruction.

The 52 gastro-enterostomies and three pyloroplasties, which are here grouped together, were accomplished with only two fatalities, one in a male infant, age two months, upon whom a Ramstedt pyloroplasty was performed,

under a mistaken diagnosis, and who died of hemorrhage from a duodenal ulcer, and the other, in a boy, age 11, who died following drainage of an hepatic abscess two months after gastro-enterostomy for pyloric stenosis

We feel the record of resections of stomach and duodenum is remarkable. There were 17 in all, with only two fatalities, one following a pyloroduodenectomy for a large, deeply penetrating juxtapyloric ulcer (Landivar, 1928), and the other, in an infant, age 22 months, with a stenosing ulcer 1 cm above the pylorus. The surgeon in the latter case (Stohr, 1925) stated that, in his opinion, a gastro-enterostomy would have sufficed.

In Table VI, the mortality rates at different ages may be seen. The chief points of interest are that the rate in the very young has been high (70 per cent), and for the adolescent child rather low (4.6 per cent).

Table VII is introduced for those who may use this article for reference. It indicates the names of the authors, the types of operations performed in the various age-groups, and the survival or death of the patient as the case may be.

Ladd's case has not been published previously. A boy, age 11, gave a history of vomiting and loss of weight of two years' duration. Roentgenologic examination showed pyloric obstruction with 50 per cent gastric retention at the end of 18 hours. A posterior gastrojejunostomy was performed in June, 1938, for an indurated pyloric ulcer. In April, 1940, the boy had gained 33 pounds in weight and was having no symptoms.

Imbassahy refers to the case of E. Mensi, the report of which we have been unable to obtain in the original (*Policlinica infantile*, January, 1935). A girl, age 13, had had attacks of headache, obstipation and vomiting. Roentgenologic studies showed a niche, characteristic of ulcer, in the duodenal bulb. She was cured by a gastro-enterostomy.

The fact should be mentioned that children are no more immune from the dangers of postoperative gastrojejunal ulcer than are adults. This is seen from the report of three cases by Michaelsson (1925). We have found two other cases of postoperative jejunal ulcer in individuals within the age-groups under discussion. One of these was described by Freund (1903), and also by Tiegel (1904), the other by Strode (1933).

SUMMARY AND CONCLUSIONS

Our rather complete examination of the literature on the subject forces us to conclude that there are a considerable number of infants and children who at one time or another have peptic ulcers of the stomach or duodenum. We believe that at ages up to and including adolescence there are a large number of unrecognized or unreported ulcers of a potentially serious nature. Probably many of the lesions are acute and superficial and heal quite rapidly when the regimen is altered in some simple manner. In a few cases, the symptoms persist and, if a study with barium is undertaken, an ulcer is found which often shows a definite crater. Roentgenologic studies should, we think, be made more often in the younger patients.

PEPTIC ULCER IN CHILDHOOD

OPERATIONS FOR PEPTIC ULCER OF THE STOMACH AND DUODENUM IN INFANTS AND CHILDREN

TABLE VII

CLOSURE OF PERFORATION		PYLOROPLASTY		GASTRO ENTEROSTOMY		RESECTION		APPENDICECTOMY		EXPLOSION ONLY	
NEW BORN	DUNHAM, THELANDER AND MATHES (0-14 days)	SMYTH, BIRD ET AL ¹	STERN ET AL ¹	NEW BORN (0-14 days)	15 days-1 year	ALSBERG, NETTELBLAD	THEILE (DE QUERVAIN)	BUFE	BECHTOLD	JOHN	LEE AND WALLS
15 days-1 year	Selinger ¹ , Rosset										
2											
3	Downes										
4											
5											
6											
7	Norrlin, Tashiro and Kobayashi										
8											
9	Lilienfeld Toal Lohr ¹										
10	Kirstad										
11											
12	Ansel and Angele, Krystad										
13	Deuticke ¹ , Gordon										
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* Recovery of patient is indicated whenever name of author is underlined
† Ac 1—Plus pyloric exclusion
2—Plus cauterization of ulcer
3—Plus cauterization of ulcer
4—Plus excision of ulcer
5—Gastro enterostomy, later two operations for closure of perforations

6—Closure, later a resection
7—Plus gastro enterostomy
8—Gastro enterostomy
9—Gastro enterostomy done later
10—Result not stated

11—Previous gastro enterostomy
12—Operation elsewhere for jejunal ulcer at later date, result not stated
13—Enterostomy later for perforated jejunal ulcer, died

For otherwise healthy infants and children with chronic hemorrhage, perforation, pyloric occlusion or uncontrollable symptoms, operation is indicated, but children, like adults, are subject to the dangers of postoperative gastrojejunal ulcer.

Recovery is reported subsequent to the closure, 34½ hours after birth, of a perforated duodenal ulcer in a colored, male infant. The child is well, six years afterward.

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SURGICAL PROBLEMS IN THE TREATMENT OF GASTROJEJUNAL ULCERATION¹

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It will probably be conceded that the operation of gastro-enterostomy still occupies an important rôle in the surgical treatment of duodenal ulcer. In the majority of instances, the patients are definitely relieved of their symptomatology, because the duodenal lesion is usually healed by this simple procedure. In any series of cases, however, there are some unsatisfactory results, patients in whom the postoperative train of symptoms is often materially worse than those which originally brought them to operation. Most of these serious complaints may be attributed to the effects of gastrojejunal ulceration. The appearance of this complication following gastro-enterostomy has long been recognized, but it is only recently that the frequency of marginal and jejunal ulceration has been fully appreciated. However, the occurrence of gastrojejunal ulceration is not solely confined to gastro-enterostomy. It may occasionally follow a gastrectomy of the Billroth II-type for duodenal ulcer.

It was thought that it might be of interest to discuss the subject of gastrojejunal ulceration as it occurs in the ward patients of a general hospital, placing special stress on the surgical problems which may complicate its treatment.

The therapeutic approach to this problem demands an intimate knowledge of the pathology and pathologic physiology induced by these lesions. It is important to know the extent, character, and location of the ulceration. There may be one or more ulcers present. These may be located in the margins of the stoma, usually on the jejunal side and rarely the gastric. Ulceration may occur opposite the stoma, or a short distance from it, most often in the efferent rather than the afferent jejunal loop. The ulcer may be either superficial, simulating an erosion, or deep, with a definite crater. In either variety, if the blood vessels are involved, hemorrhage may be a serious complication. While the jejunal and marginal ulcers may perforate either into the free peritoneal cavity or into the colon, causing a gastrojejunocolic fistula, it is more usual for these penetrating ulcers to be effectively walled-off by the adherence either of the transverse mesocolon, the colon, intestines, or pancreas. This may result in a large intra-abdominal inflammatory exudate.

Occasionally, the inflammatory reaction about an area of ulceration may be so severe and extensive that either an acute or subacute obstruction of the gastro-enteric stoma or the efferent loop may result. In some cases, even

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though this acute inflammation eventually subsides, the resulting scar tissue may produce some degree of obstruction. Obstruction in the stomal region, especially if accompanied by either a pyloric spasm or a duodenal stenosis usually produces a dilatation of the stomach. The gastric wall under these circumstances may eventually become atonic. The resulting inability to retain food, and the loss of gastric secretions by vomiting lead to nutritional disturbances such as an avitaminosis and an hypoproteinemia and to dehydration and an alkalosis which may become so severe as to threaten life.

The symptomatology of this disease as a rule is rather typical, and the diagnosis of gastrojejunal ulcer rarely occasions great difficulty. There is the usual antecedent ulcer history for which a gastro-enterostomy or a partial gastrectomy was performed, a few weeks or many years before the onset of the present trouble. This is described as a recurrence of the epigastric pain often so severe in its radiation to the back that morphine is required for its alleviation. Food usually aggravates the condition, with the result that appetite becomes less and weight is lost. Occasionally, the element of pain, especially in the hyposensitive individual, is overshadowed by the sudden occurrence of either a profuse hematemesis or a marked melena. While these hemorrhages may be alarming, they rarely lead to a fatal issue. Acid eructations, persistent nausea, and occasional vomiting, especially after the ingestion of food are frequent symptoms. Vomiting, however, may be a presenting and persistent symptom in the presence of stomal obstruction and gastric ileus.

The sudden occurrence of fecal vomiting, foul eructations, and persistent diarrhea, with or without antecedent pain, usually heralds the perforation of a jejunal ulcer into the transverse colon. This is a very serious complication for, unless the gastrojejunal fistula is corrected surgically, death from inanition will result quite rapidly.

Occasionally, the onset of terrific abdominal pain associated with nausea, vomiting, and the physical findings of shock, board-like rigidity, and generalized tenderness of the abdomen make a diagnosis of a perforated jejunal ulcer most likely. While a plain roentgenogram of the abdomen will not always disclose the presence of free air under the diaphragm, an abdominal puncture will invariably yield the presence of bile-tinged fluid.

Roentgenographic studies following the ingestion of a barium meal are invaluable in confirming the clinical diagnosis. These may be of inestimable aid in planning a therapeutic course. Their interpretation, to be sure, often requires unusual skill. Tenderness in the region of an irregular stoma while the patient is being fluoroscoped, a dilated stomach with retention of barium, suggestive of hypomotility or obstruction, the presence of barium patches in the jejunum, indicative of ulcer pockets, a stenosis or irregularity of either the afferent or efferent loops are helpful in the establishment of a diagnosis. The passage of a barium meal directly from the stomach outlining the colon concretely establishes the presence of a gastrojejunal fistula.

Gastroscopic examination with the flexible Schindler instrument has proved of considerable value in many of the more obscure cases. Areas of

either actual gastrojejunal ulceration or the presence of scarring about the stoma may be distinctly seen. In addition to this, the presence of either an acute or chronic gastritis may aid in differentiating the clinical picture.

Fractional test meals are of confirmatory value because in the majority of these patients who have a constitutional tendency to develop ulcers the total acidity and free hydrochloric acid are usually high. Gastrojejunal ulceration in the presence of an anacidity is almost unknown. A study of the blood plasma chlorides and the CO_2 combining power are important, for occasionally a severe alkalosis may be present without clinical manifestations.

The physical examination rarely discloses anything definite except deep supra-umbilical tenderness slightly to the left of the median line.

Once a diagnosis has been made of a gastrojejunal ulcer following either a gastro-enterostomy or a partial gastrectomy, any of the accepted medical methods of ulcer therapy should be tried first. These patients cannot be treated satisfactorily by ambulatory methods. Hospitalization with absolute bed rest must be insisted upon, if there is any possibility of effecting a "medical cure." If hemorrhage is present as a complicating factor, treatment either by absolute gastric rest and blood transfusions or by the diet advocated by Muelengracht may be tried. In cases of a gastric or a high jejunal obstruction with alkalosis, daily lavages of the stomach and the parenteral administration of adequate amounts of saline, glucose, and blood are essential. In cases of gastric atony, the return of gastric tone can best be estimated by a diminution in the amount of gastric retention, the elevation of the blood chlorides to normal, and a reduction in the CO_2 combining power of the plasma.

Many of these patients are undoubtedly healed by medical treatment, if not permanently at least temporarily, and many are improved following a course of treatment, thereby becoming better risks for operation. However, if medical treatment after a fair trial does not give satisfactory relief, or if the economic situation of the patient is such that the pattern of life cannot be made to conform with the dietary demands involved and with the routine of treatment prescribed, or if acute obstructive complications incident to jejunal ulceration are present, surgery is indicated.

Naturally, if an acute jejunal ulcer perforates into the free peritoneal cavity, immediate surgery is required, and if the perforation occurs into the transverse colon, intervention is indicated as soon as the physical condition of the patient will permit.

The surgical management of gastrojejunal ulceration and its complications depends mainly upon the pathology present at the time of operation, the surgical procedure naturally being adapted to the physical condition of the patient. With this as a basis, it may be convenient to divide arbitrarily these cases into certain groups:

- (1) Acute perforated gastrojejunal ulcers
- (2) Resectable gastrojejunal ulcers following gastro-enterostomy
- (3) Massive gastrojejunal ulcers following gastro-enterostomy

- (4) Cicatrized gastrojejunal ulcers following gastro-enterostomy
- (5) Resectable gastrojejunal ulcers following partial gastrectomy
- (6) Gastrojejunal ulcers following radical subtotal gastrectomy
- (7) Gastrojejunocolic fistulae

(1) *Acute Perforated Gastrojejunal Ulcers*—The symptomatology and physical findings of this condition are similar to that seen in perforated gastroduodenal ulcers. Once this diagnosis has been established, surgical exploration is indicated immediately. A small ulcer in the efferent jejunal loop, close to the gastro-enterostomy stoma, which has perforated into the free peritoneal cavity is usually found without difficulty. A simple closure of the perforation was all that was attempted, more radical surgery being left for the future (Case 1).

Case 1—History No 429566 B W, age 54. Admitted May 20, 1940. Died May 30, 1940.

1935—Posterior gastro-enterostomy for duodenal ulcer.

1938—Suture of a perforated gastrojejunal ulcer.

1940—Subtotal gastrectomy, with antecolic Hofmeister terminolateral gastrojejunostomy and jejunorrhaphy for jejunal ulcer, and Witzel jejunostomy.

In 1935 a posterior retrocolic gastro-enterostomy had been performed because of a duodenal ulcer. He was completely relieved of symptoms following this operative procedure until two weeks before admission, when he had a recurrence of epigastric pain coming on three or four hours after meals. On the morning of admission, September 13, 1938, he was suddenly seized with severe generalized abdominal pain which steadily increased in severity. There was nausea but no vomiting. A right inguinal hernia and absent testicle had been known for many years. Following the attack of pain, the inguinal mass became larger than usual, painful, and could not be reduced. He was admitted to the service of Dr. A. Hyman.

Physical examination revealed an acutely ill, prostrated male. The teeth were carious. The lungs showed diffuse musical rales, heart slightly enlarged. Blood pressure 130/90. Abdomen was generally spastic, more so in the lower quadrants, right greater than left. There was also generalized abdominal tenderness, and rebound. There was a tender mass in the right inguinal canal which could not be completely reduced. Right testicle was absent from the scrotal sac. No obliteration of liver dullness. White count 23,900, with 81 per cent polys. Hemoglobin 92 per cent. Urine negative.

The differential diagnosis lay between torsion of an intra-abdominal testicle or perforated gastrojejunal ulcer. Celiotomy was immediately performed through a right lower quadrant midrectus incision, which exposed the external ring. An hemorrhagic, inflamed hernial sac was visualized. The sac was mobilized and opened, revealing large quantity of greenish fluid. A small testicle was seen and resected, herniorrhaphy performed, and then the upper abdomen was explored, which disclosed a perforation of a gastrojejunal ulcer. Repair was effected. Patient's postoperative course was remarkably good, and he was discharged on the fourteenth postoperative day, April 27, 1938.

He continued to complain of abdominal pain after meals and was readmitted, May 20, 1940, at which time Rehfuess test meal showed a free acid of 80 and total of 90 units. Roentgenograms revealed the presence of a jejunal ulcer and a 40 per cent gastric residue after three hours. He was reexplored, under spinal anesthesia. The stomach was dilated to two and one-half times its normal size. On the anterior wall of the jejunal side of the stoma, a penetrating jejunal ulcer, sealed-off by a thickened transverse mesocolon, was found. A subtotal gastrectomy with an antecolic Hofmeister terminolateral gastrojejunostomy, and an excision of a jejunal ulcer, with a jejunorrhaphy was performed.

Because of the atonic stomach, a Witzel jejunostomy was done. He developed a bronchopneumonia of both lower lobes. Sulfapyridine was given in full doses through the jejunostomy, as well as Type III antipneumococcus serum. He died three days after operation. P. M. No. 70865. Confluent bronchopneumonia.

(2) *Resectable Gastrojejunal Ulcers Following Gastro-enterostomy*—An adequate preoperative preparation of these patients, as well as all groups suffering from this disease is most essential. Careful attention was paid to the oral hygiene. The diet was adequate in its protein and vitamin content. Sufficient fluids were given by mouth, supplemented if necessary by the parenteral administration of saline, glucose, and blood. If gastric retention was not present, the stomach was lavaged only once, *ie*, six hours before operation.

There appears to be no ideal anesthesia because, regardless of the method, the incidence of pulmonary complications is unfortunately extremely high, and often the cause of death. Our best results seemed to have been obtained with spinal anesthesia with Jones' solution, combined with pentothal intravenously. In cases which were unusually poor risks, a field block of the upper abdominal wall with novocain was supplemented by either cyclopropane or ethylene anesthesia.

Past experiences with the surgery of gastrojejunal ulcers have taught us that if better and more satisfactory follow-up results are to be expected, certain operative procedures must be discarded. Excision of the marginal and jejunal ulcers with some type of plastic repair, another gastro-enterostomy in addition to the existing one, and separation of the old gastro-enterostomy with the formation of a new one, are of little permanent value in the presence of active ulceration. Under certain circumstances, these palliative procedures may prove useful until the condition of the patient improves sufficiently to tolerate more radical surgery. Simple separation of the gastro-enterostomy stoma and the excision of the jejunal ulcer as a definitive procedure in the treatment of gastrojejunal ulceration is ultimately unsatisfactory in most instances. It is invariably followed by a reactivation of the duodenal ulcer, or possibly a gastric ulcer, with a recurrence of all the previous symptoms (Case 2).

Case 2—History No. 453891. A. B., age 38. Admitted March 18, 1940. Discharged March 31, 1940.

1920—Gastro-enterostomy for duodenal ulcer.

1940—Disconnection of gastro-enterostomy, gastrorrhaphy, and jejunorrhaphy for jejunal ulcer.

1940—Subtotal gastrectomy with Hofmeister terminolateral gastrojejunostomy (antecolic) for duodenal ulcer.

This is the fourth admission of a male who had had a gastro-enterostomy performed in 1920 for a duodenal ulcer. He remained well until 1934, when he developed upper abdominal pain, and the following year roentgenography revealed a marginal ulcer. He was relieved by medical therapy until 1939, when the pain recurred, this time accompanied by bleeding. Since then, he has had epigastric pain intermittently. A gastro-intestinal series taken in August, 1939, and in January, 1940, revealed an incomplete

obstruction and an ulcer in the distal jejunal loop, about two inches from the stoma. There was a small three-hour retention.

Physical examination revealed an obese but well-developed male. Blood pressure 126/60. There was tenderness in the right upper quadrant and epigastrium, and scars of previous operations for bilateral inguinal herniae, and of the previous gastro-enterostomy. Hemoglobin 96 per cent. There was a gastric retention of 100 cc. The Rehfuß test meal showed a 44 free acid, and total of 52 units. The fasting contents contained a free acidity of 10, and total of 40 units. Blood urea 12 mg, blood sugar 116 mg, plasma chlorides 620 mg, carbon dioxide 48 vol per cent. The blood Wassermann was negative. The urine was negative.

Exploration was performed, under avertin and ethylene anesthesia, March 21, 1940, through a median epigastric incision. The stomach and duodenum were found adherent to the previous right epigastric incision. The gastro-enterostomy stoma was markedly narrowed, evidently from previous ulceration. There was definite constriction of the efferent loops with marked dilatation of the afferent. The region of the duodenum was friable and showed signs of old healed ulceration. The gastro-enterostomy was disconnected. A gastrorrhaphy was performed. The jejunal ulcer was excised and a transverse jejunorrhaphy was done. Because the condition of the patient was not entirely satisfactory at this stage, no further surgery was attempted.

The postoperative course was satisfactory. He was discharged on the tenth day after operation.

Patient was well for about two months after his operation, and then developed a recrudescence of the symptoms resembling his previous duodenal ulcer. A Rehfuß test meal showed a free hydrochloric acid of 40, and a total of 70 units.

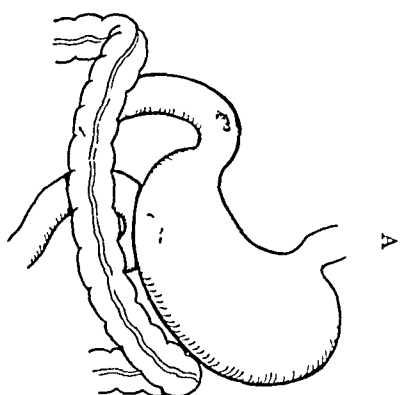
He was readmitted in June, 1940, at which time a subtotal gastrectomy of the Hofmeister type, with a terminolateral gastrojejunostomy was performed for chronic gastric ulcer. Following this he made an uneventful recovery.

When last seen, January 8, 1941, he had no further complaints.

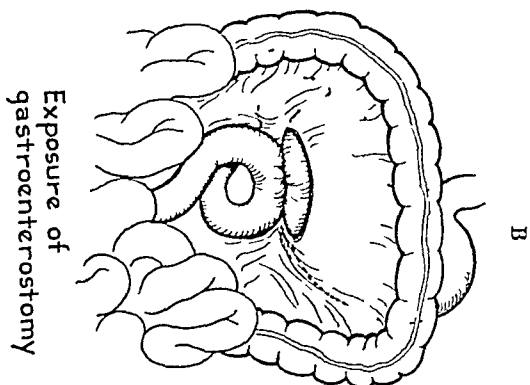
Therefore, in the surgical treatment of gastrojejunal ulcers an attempt should be made to insure the patient, if at all possible, against subsequent ulceration in the stomach, duodenum, or jejunum. Ulceration in these areas is not apt to occur in the presence of an anacidity. Anacidity, or low acid values, are most frequently obtained by an excision of the acid stimulating pylorus and antrum, and as much of the acid secreting fundic portion of the stomach as possible. The resection of the diseased area involved in the gastrojejunal ulceration, supplemented by a radical subtotal gastrectomy of the Billroth II-type theoretically, and at present, best fulfills this requirement.

The performance of a primary subtotal gastrectomy is not an easy technical procedure at best, but in the presence of a gastrojejunal ulceration, it is fraught with innumerable additional dangers—hazards which can only be partially eliminated with increased experience and particular attention to surgical minutiae. The operation should be so planned that it may be successfully terminated at certain stages should the physical condition of the patient not warrant its completion (Case 2). For this reason we have divided the operation into two main parts. I. The separation of the gastro-enterostomy. II. Subtotal gastrectomy.

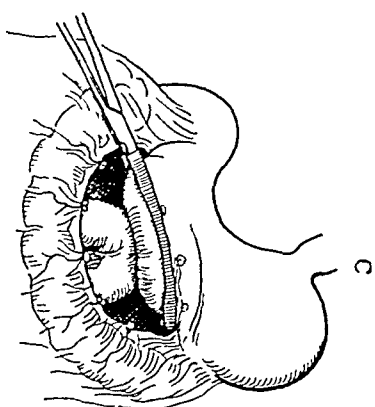
- I Separation of the gastro-enteric anastomosis, followed by
 - (a) Gastrorrhaphy



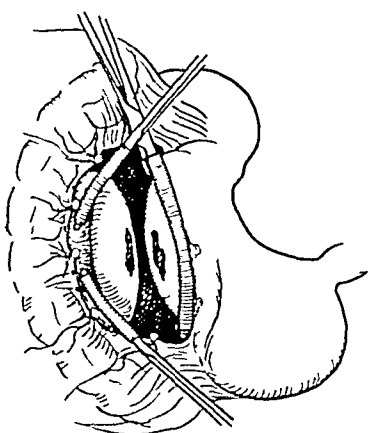
Posterior gastroenterostomy
for duodenal ulcer



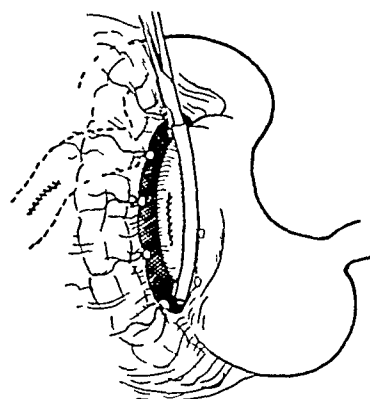
Exposure of
gastroenterostomy



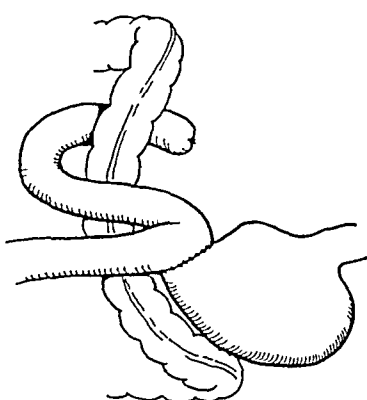
Exposure of liberated stoma
through the lesser omental sac



Separation of stoma



Gastrorrhaphy and
jejunorrhaphy



Hoffmeister subtotal gastrectomy
with antecolic termino-lateral
gastrojejunostomy

D
Figs 1—D) illustrating the operative procedures employed in the separation of the
gastric stoma

(b) Excision of the jejunal ulcer with restoration of jejunal continuity by

- (1) Jejunoirrhaphy
- (2) End-to-end jejunojejunostomy
- (3) End-to-side jejunojejunostomy
- (4) Side-to-side jejunojejunostomy

2 Subtotal gastrectomy of the Hofmeister-type with terminolateral gastrojejunostomy either anterior or posterior to the transverse colon

I *Separation of the Gastro-enteric Anastomosis* —(a) In order to identify the retrocolic posterior gastro-enterostomy (which was the most common type of previous procedure) the greater omentum was completely freed from the adhesions which invariably bound it to the previous abdominal incision and other intra-abdominal viscera. Following this, it was possible to bring the transverse colon and its mesentery upward and forward, thereby exposing the jejunal portion of the stoma. Then, the field of operation was carefully walled-off and protected by hot moist pads. The dense adhesions in this area were carefully divided by knife dissection, liberating the afferent and efferent jejunal loops. The anterior margin of the adherent transverse colon was dissected free, exposing the gastric side of the stoma (PLATE I B). Frequently while liberating the anterior part of the anastomosis, areas of acute ulceration were entered, with the escape of intestinal content. If perforation did occur, it was temporarily closed by sutures. At this point, we usually found it advisable to enter the lesser omental sac by horizontally dividing the gastrocolic omentum in the region of the stoma. The anastomosis was then more easily mobilized laterally, and posteriorly from its attachment to the transverse mesocolon, great care being taken to preserve the integrity of the middle colic vessels. If ulceration was present in this location, the resulting edema and induration often caused a thickening of the transverse mesocolon with marked distortion of the normal anatomy. Once the anastomosis was freed completely, it could be easily delivered through the lesser omental sac, provided the afferent jejunal loop was sufficiently long (PLATE I C). If this loop was short, the anastomosis was drawn downward below the transverse mesocolon so that it could be adequately controlled during its separation.

The stomach was then carefully separated from the jejunum, "spilling" being avoided either by the application of a curved rubber clamp to the bowel or the judicious use of suction (PLATE I D). The gastric opening was immediately closed with a Connell inversion suture of chromic catgut reenforced with a continuous Lembert-Pagenstecher suture (PLATE I E). This step, if a gastrectomy was to be subsequently performed, may appear unnecessary to some, but it is an added precaution in the maintenance of peritoneal asepsis.

(b) Excision of the jejunal ulcer and restoration of jejunal continuity. The disconnected loop of open jejunum was then carefully inspected. If the ulcer was small, the lesion was excised locally, and in many instances the entire mesenteric border of jejunum was left undisturbed. In cases such as these, a transverse jejunoirrhaphy restored the lumen of the bowel (PLATE I

E) However, partial jejunectomy became necessary when the ulceration either involved the circumference of the bowel or penetrated into its mesentery. Extensive scarring with stenosis of the bowel occasionally called for an intestinal resection.

Jejunojejunostomy, similar to intestinal anastomosis, is beset with two great dangers—leakage and obstruction at the site of the anastomosis. Leakage may be prevented by the careful preservation of the blood supply to the bowel and the accurate surgical approximation of its walls. Obstruction may be partially eliminated by selecting that type of anastomosis which will insure an adequate lumen, thereby eliminating the possibilities of obstruction with the serious sequelae of back pressure on the duodenal and jejunal suture lines. An end-to-end anastomosis was the most frequently used procedure. Occasionally, in the presence of a reticocolic, no-loop, posterior gastrojejunostomy, certain technical details made this type of jejunal restoration impractical. The proximity of the anastomosis to the ligament of Treitz, and the duodenojejunal angle, increased the hazards of an end-to-end suture. Under these circumstances, we have implanted the open end of proximal jejunum into the side of the distal jejunum (Case 3). In other cases, when a marked disparity existed in the diameter of the afferent and efferent jejunum, a side-to-side anastomosis was performed (Case 6).

A certain amount of local edema is apt to follow any type of intestinal anastomosis. Some surgeons have advocated the introduction of either a Levin tube or its modification through the new gastrojejunostomy and *via* the jejunojejunostomy to the region of the duodenal stump, in order to reduce the accumulation of gas and fluid in this blind end. Theoretically, this may be a good suggestion, but, practically, we have found it difficult, and at times impossible, to thread effectively a Levin tube along this devious channel and maintain strict asepsis.

Occasionally, following the separation of the gastrojejunal anastomosis and closure of the gastric defect and the restoration of jejunal continuity, the physical condition of the patient did not safely permit further surgery. The operation was then terminated successfully at this point, after the closure of the rent in the transverse mesocolon and the gastrocolic omentum (Case 2). However, in the average case, it was usually possible to proceed with the subtotal gastrectomy.

II Subtotal Gastrectomy—This part of the operation rarely presented unusual difficulty. The technic which was followed was essentially that which has been previously described by Dr. A. A. Berg.¹ The stomach was usually transected at a point well proximal to the ileocecal angle, and high on the greater curvature. The resection must be radical, subtotal in its extent; any lesser resection, we feel, is to be condemned. While it is undoubtedly important to measure the gastric segment which has been resected, it is more important to leave as little of the stomach as is consistent with safety. Inasmuch as the previous gastro-enterostomy has usually healed the duodenal ulcer, the excision of the ulcer-bearing area, and closure of the distal duodenum were

usually quite simple. The duodenal stump was regularly drained with rubber dam, which was brought out through a right subcostal stab wound. There were no cases in which any postoperative complications could be ascribed to the drainage. However, there were a few in which a small duodenal leak was effectively drained externally, thereby preventing the hazards of a generalized peritonitis.

Gastro-intestinal continuity was restored by the Hofmeister modification of the Billroth II-type of procedure, with a terminolateral gastrojejunostomy. Whether this anastomosis was made either anterior or posterior to the colon seemed to be of little importance. No difficulties have been noted either in the immediate postoperative course or in the follow-up observations of either type of anastomosis. We are at present employing the anterior type more, because if further gastrojejunal ulceration should develop, the technical difficulties of any subsequent surgery are definitely lessened (PLATE I F).

The abdominal incision, usually a median epigastric one, was closed with interrupted, through-and-through heavy silk sutures. This type of closure has been employed for many years, and has proved to be an excellent prophylactic measure against wound dehiscence and evisceration.

Following the return to the wards, the Levin tube, which was introduced intranasally into the stomach at the time of operation, was aspirated every two hours. Parenteral fluids, which were administered throughout the operation, were continued, supplemented by blood transfusions if necessary. Fluids were allowed by mouth after 24 hours. Intravenous saline and the Levin tube were discontinued when sufficient quantities of fluid were taken by mouth, and were retained.

(3) *Massive Gastrojejunal Ulcers Following Gastro-enterostomy*—

There were certain types of gastrojejunal ulcers in which persistent vomiting, resulting in alkalosis, was a prominent symptom. After the adequate pre-operative preparation already referred to, exploration was performed. Often an active penetrating ulceration was found which caused an extensive productive inflammatory reaction in the neighborhood of the anastomosis, resulting, occasionally, in either an acute or subacute obstruction in the region of the stoma. Any radical surgery entailing extensive dissection in this acutely infected, friable, and edematous tissue would probably have caused a rapid spread of a fatal peritonitis. In conditions such as this, we have been ultra-conservative. A Witzel jejunostomy was performed for alimentation and as a palliative procedure (Case 3). Jejunal feedings of proper content and sufficient caloric requirement usually caused a definite physical improvement in these patients. Gastric digestion was practically eliminated, giving the stomach a certain amount of physiologic rest. In the interim, a period of four to 12 weeks, the marked inflammatory reaction which was previously present about the area of ulceration either subsided, or the ulcers were healed completely, so that at the time of reexploration, a previously inoperable condition became operable. A subtotal gastrectomy could be performed now without undue risk. Many surgeons have condemned jejunostomy

because it may result in leakage with a fatal peritonitis, and occasionally in acute intestinal obstruction. If a jejunostomy is properly performed there should be no danger from either of these two complications. It is important, however, that the jejunostomy be performed at least 18 to 22 inches from the duodenal angle and that the enterostomy tube be brought out through a left subcostal stab wound. These precautions eliminated any interference with a subsequent subtotal gastrectomy. Following this operation the jejunostomy tube may be removed as soon as gastric alimentation is restored.

Case 3—History No 432385 L. K., age 55. Admitted November 29, 1938. Discharged April 2, 1939.

1915—Suture of a perforated gastric ulcer, with posterior retrocolic gastro-enterostomy (January).

1915—Excision of a duodenal ulcer, with pulse-string occlusion of the pylorus (August).

1916—Exploratory celiotomy for high intestinal obstruction, due to multiple adhesions.

1938—Jejunostomy for alimentation, because of pyloric stenosis, with occlusion of the gastro-enterostomy stoma by massive jejunal ulceration (December).



CASE 3—Roentgenogram demonstrating massive jejunal ulceration with penetration

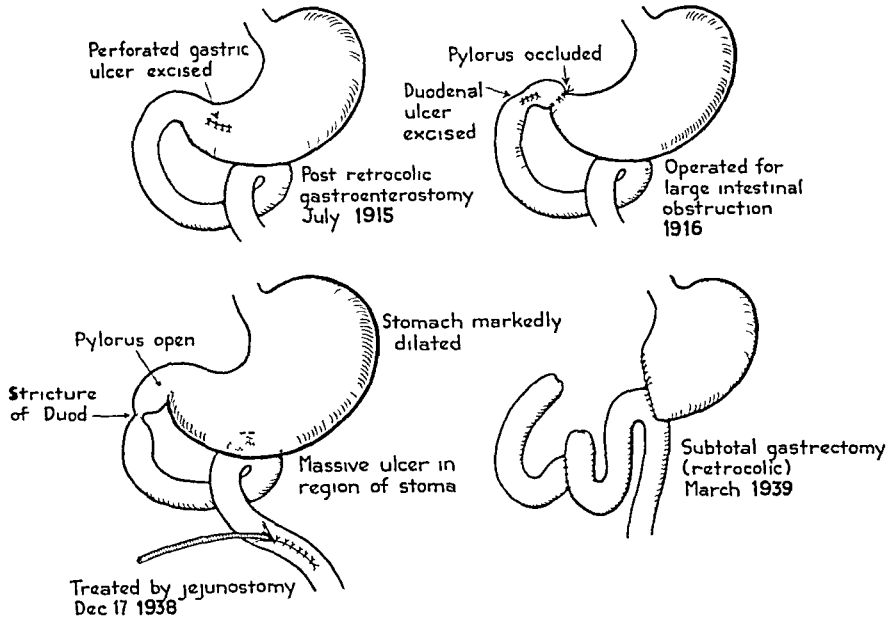
1939—Subtotal gastrectomy, with posterior retrocolic terminolateral gastro-enterostomy of the Hofmeister type, and partial jejunectomy, with end-to-side jejunojejunostomy for healed gastrojejunal ulcer (March).

This is the first admission of a male, age 55, who for the past 24 years has had ulcer symptoms. In 1914, an appendicectomy was performed for chronic appendicitis. In January, 1915, he perforated a gastric ulcer and at that time, in addition to a suture of the ulcer, a posterior retrocolic gastro-enterostomy was performed. In August, 1915,

he was reexplored because of persistent ulcer symptoms and at that time a small ulcer on the anterior wall was excised and a purse-string occlusion of the pylorus was performed. In 1916, he was again operated upon because of high intestinal obstruction, due to multiple adhesions. He was then well until about three months before admission, when he began to have recurrence of his ulcer pain, and two weeks before admission there was persistent nausea, vomiting, and severe abdominal cramps.

Physical examination disclosed a man, cadaverous in appearance, in marked distress, complaining of severe cramp-like abdominal pain. Teeth were in poor condition and there was marked pyorrhea. Abdomen was soft. There was acute epigastric tenderness.

#432385



CASE 3—Schematic view of operative procedures

The scars in his left upper quadrant and upper midabdomen, and lower right quadrant were well healed. Hemoglobin 75 per cent. Blood pressure 105/70. Blood urea 25 mg., blood chlorides 505 mg., CO 71 vol per cent. Total blood proteins 5.6. Blood Wassermann was negative. Urine examinations were negative, and the stools were four plus guaiac. A Rehfuess test meal showed free acid of 55 units and total acidity of 75, and blood was present. A gastro-intestinal series showed marked pyloric stenosis and a very narrow and deformed gastro-enterostomy stoma, with a definite pocket in the jejunum just distal to the stoma. There was marked residue after six hours. Gastroscopy revealed that the gastro-enteric stoma was patent, and there was a marked atrophic and marked localized hypertrophic gastritis. Lavage of his stomach on several occasions revealed retention of 1,000 to 3,000 cc. Because of the persistence of his vomiting, the marked retention, the intractable pain, and the fact that he was losing ground, surgical exploration was performed, December 7, 1938, under local anesthesia and ethylene. The stomach and transverse colon were dissected from the anterior abdominal wall and from the under-surface of the liver. A lesion about the size of a large walnut was found in the region of the gastro-enterostomy stoma, evidently due to a posterior jejunal ulcer. Because of the marked inflammatory reaction which was present and poor surgical condition of the patient, a Witzel type of jejunostomy for jejunal alimentation was performed about 18 inches from the gastro-enteric stoma, and the tube was brought out through a left subcostal stab incision.

The patient did not do well immediately after operation because of severe infection.

of the anterior abdominal wall, and in addition to his jejunal feedings of Scott-Ivy pabulum he was given supportive treatment of blood transfusions and glucose intravenously. Following rest and gastric lavage, the retention gradually diminished. Gastros-copy at this time showed a slight improvement, inasmuch as there was less inflammatory reaction about the stoma. A gastro-intestinal series at this time showed that the jejunal ulcer which had been previously noted was definitely smaller and, although there was still more than 50 per cent residue at the end of six hours, much barium was seen to pass through the pylorus.

His general condition improved sufficiently so that about three months after the preliminary jejunostomy he was reexplored, March 8, 1939. The stomach was again found adherent to the anterior abdominal wall, as well as the omentum. The duodenum was adherent to the under surface of the liver. The stomach was dilated to two and one-half times normal size, and its walls were markedly atrophic. About one-half inch distal to the pylorus, there was a marked stenosis of the duodenum, evidently the site of the previously excised ulcer. In the region of the gastro-enterostomy stoma, the afferent loop was especially short and dilated, and at a point slightly distal to the stoma there was a definite stenosis, almost leading to a complete occlusion of the efferent loop. About six inches farther along, there was a kinking of the jejunum. The marked inflammatory reaction which had been noted at the previous exploration had completely disappeared. There was no evidence of an active jejunal ulcer. All that remained was a scar almost occluding the efferent jejunal loop. A subtotal gastrectomy, with Hofmeister termino-lateral retrocolic gastrojejunostomy was performed for a healed duodenal ulcer, and a partial jejunectomy, with an end-to-side jejunojejunostomy, was performed for a healed jejunal ulcer of the efferent loop.

The postoperative course was fairly smooth, the only complication being a mild wound infection. Jejunostomy was maintained for feeding purposes until the patient could take adequate diet by mouth, and the enterostomy tube was removed 11 days after operation. He has been unusually well, and has gained almost 40 pounds. He has had no symptoms referable to his gastro-intestinal tract when last seen, April 10, 1940.

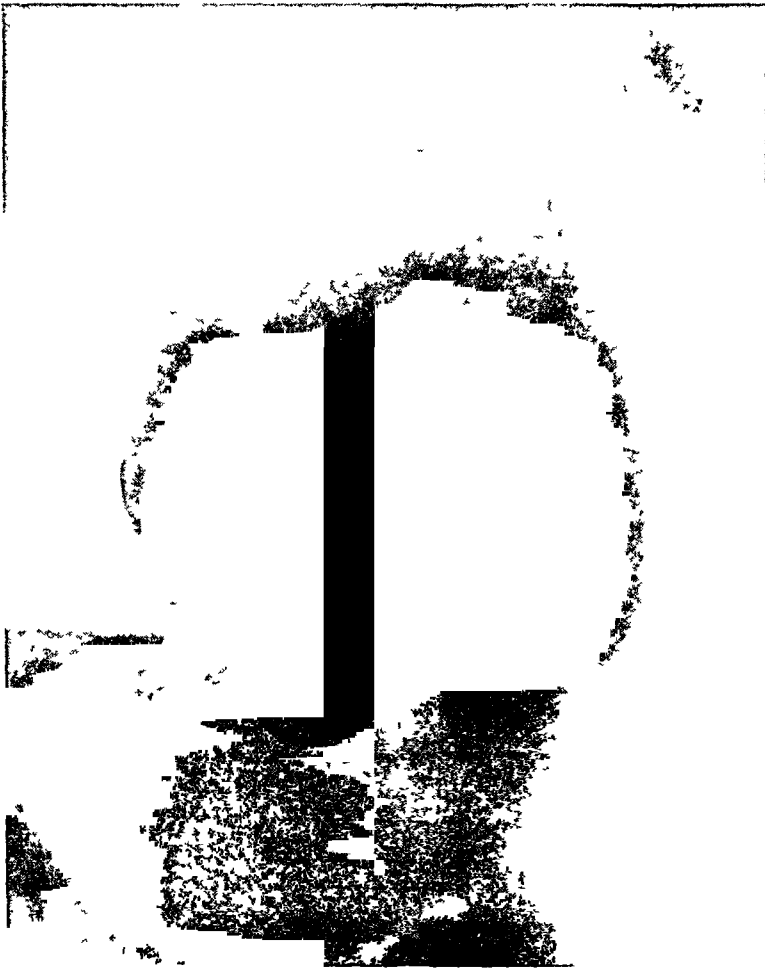
(4) *Treatment of Cicatrized Stomal and Jejunal Ulcers Following Gastro-enterostomy*—This group usually was in urgent need of surgery. These were the patients who were not suffering solely from the effects of acute ulceration, but rather from the effects of gastric obstruction incidental to the cicatricial contraction of marginal and efferent jejunal ulcers. These patients, as a rule, were so dehydrated and debilitated by long periods of intermittent vomiting that even if the chemical imbalances were adequately corrected, the shock of any extensive surgery would have terminated disastrously. In this group, either some simple corrective measure aimed to relieve the obstruction, or a jejunostomy for alimentation was performed in order to temporarily relieve the patient until an improved physical condition would permit more radical surgery, should it be deemed necessary. If, at the time of exploration, the pylorus was patent and the extensive scarring of previous jejunal ulceration had produced a stenosis of either the stoma or the efferent jejunal loop, a properly placed entero-enterostomy appeared to be all that was necessary to relieve the symptoms. The physical condition of the patient improved following this simple procedure. If active jejunal ulceration should recur subsequently, radical surgery could be undertaken then under more auspicious circumstances (Case 4).

Case 4—History No 439460 W E, age 60 Admitted May 12, 1939 Discharged June 25, 1939

1919—Posterior retrocolic gastro-enterostomy for bleeding duodenal ulcer

1923—Appendicectomy for chronic appendicitis

1939—Jejunojejunostomy for obstruction of distal jejunal loops, due to jejunal ulcer



CASE 4 —Roentgenogram showing obstruction of efferent jejunum, with marked dilatation of stomach, duodenum and afferent jejunum

This is the first admission of a patient who, since age 16, has had multiple episodes of epigastric pain which were usually followed by hematemesis and black stools. These occurred at intervals of six to eight months. Twenty years ago, he had had a posterior gastro-enterostomy for duodenal ulcer. Four years later, after a severe hemorrhage, he had another celiotomy, at which time a diseased appendix was supposed to have been removed. Three years before this admission he was treated at another hospital for massive hemorrhages. Four months before the present admission he began to complain of severe epigastric pain radiating to the right upper quadrant, nausea, and vomiting. The vomitus consisted of the food ingested from previous meals. Five weeks before admission he had a severe hemorrhage.

Physical examination disclosed a rather pale and chronically ill male. There was moderate peripheral sclerosis. Blood pressure 140/80. There was tenderness and pressure in the epigastrium and a well-healed upper right rectus scar extending from the ensiform to below the umbilicus. Hemoglobin 67 per cent. RBC 3,900,000. WBC 3,000.

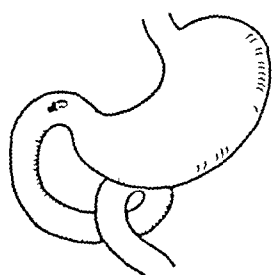
with normal differential Sedimentation time one hour, four minutes Urine Specific gravity 1036, faint trace of albumin, occasional hyaline casts Blood urea 11 mg, blood sugar 100 mg, blood chlorides 620 mg, the CO_2 combining power 75 vol per cent Icteric index 6, total blood proteins 57 mg The Rehfuess test meal free acid 35 units, total acidity of 48 Electrocardiogram showed slight depression of the RT transition in leads II and III

A gastro-intestinal series showed a gastro-enterostomy The barium which was ingested almost all passed to the proximal loop, causing the duodenum to become markedly dilated The duodenal bulb was markedly deformed The first one and one-half inches of distal jejunum was markedly narrowed, and showed the presence of a small ulcer pocket At the end of six hours there was a 20 per cent residue

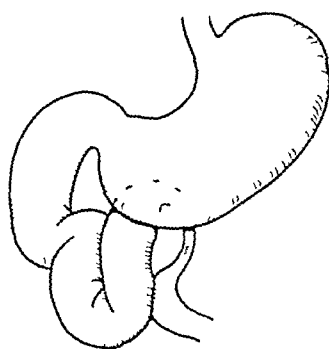
The gastric retention was treated conservatively with lavage, and intravenous fluids were administered liberally Retention was markedly diminished, and after two transfusions, hemoglobin was elevated to 80 per cent

On May 7, 1939, an exploratory celiotomy was performed, under local field-block and ethylene There were innumerable adhesions from the omentum to the anterior abdominal wall The stomach in the region of the pylorus and duodenum was adherent to the under surface of the liver by fine, dense adhesions, which were freed There was

#439460



Posterior
gastroenterostomy
for duodenal ulcer
1918



Jejunojejunostomy
for stenotic ulcer of
distal jejunal loop
1939

Cast 4—Schematic review of operative procedures

no evidence of any active duodenal ulcer On turning the transverse colon upward, adhesions were found completely occluding the afferent and efferent loops leading to the gastro-enterostomy Upon freeing these, the stoma was exposed On the anterior wall of the jejunum, occupying mainly the efferent loop, was a definite, acutely inflamed, jejunal ulcer which almost completely occluded the lumen, causing dilatation of the afferent loop to about four times normal size Beyond the area of ulceration, the efferent loop appeared normal A side-to-side jejunojejunostomy was performed between the dilated afferent and the small efferent loop, and about ten inches from this anastomosis a typical Witzel jejunostomy was performed for jejunal alimentation

Following operation, gastric retention and alkalosis receded within three weeks He had slight pitting edema of the ankles, at which time blood chlorides were about 610 mg Parenteral saline was stopped at this point, and the edema disappeared, and blood chlorides fell to about 540 mg

One month after operation, a gastro-intestinal series showed much less distention of the proximal loop of the jejunum and duodenum The first one and one-half inches of the distal loop was constricted but no ulcer pocket was visible There was no gastric retention He was discharged asymptomatic on a Muelengracht diet, without any pain

He was subsequently readmitted, August 8, 1939, and discharged on September 10, 1939, because of tarry stools Following the operation he did well and gained 35 pounds

During the two months he was at home, he followed a strict diet and gained in weight. He experienced an episode of dizziness, hematemesis and melena on admission. He was well-developed and well-nourished, rather pale. Blood pressure 120/80, pulse 96. Hemoglobin 62 per cent, RBC 4,400,000, WBC 14,000 with a normal differential. Stools were guaiac positive. Urea 46. Urine was negative. Total protein 61. Hemoglobin dropped to 52 per cent, then to 42 per cent in the next few days, and he continued to have positive stools. Stools became guaiac negative on the thirteenth day, and the hemoglobin began to rise following four transfusions. He was placed on a Muelengracht diet while he was in the hospital. Surgery was not advised at this time.

When last seen, January 22, 1941, he had gained 46 pounds since operation, and looked amazingly well. He had no complaints.

There were instances in which the gastro-enteric anastomosis had become almost completely obliterated by extensive scarring, and, as a result, a new ulcer appeared with reflex pylorospasm. In this type of case in which the condition of the patient was poor, the jejunum was easily separated from the stomach and its continuity was rapidly repaired, and a new gastro-enterostomy was performed. This appeared to be effective (Case 5). If, in addition either to the gastrojejunal obstruction, a pyloric spasm or a duodenal stenosis was present, the problem of a marked gastric dilatation complicated the picture. An adynamic gastric ileus as a postoperative complication is most serious. The constant retrograde drainage of duodenal contents into a dilated gastric pouch, often for weeks, is bound to result in marked intestinal disturbances and alkalosis. Under these circumstances, the operation of gastro-enterostomy was supplemented by a Witzel jejunostomy for alimentation. Many surgeons in preference to jejunostomy, introduce a two-way tube at the time of gastro-enterostomy through the stoma into the efferent jejunum so that one part drains the stomach while the other part may be used for alimentation. Under ordinary circumstances, this tube is of undoubted value, but in conditions such as these described it possesses certain disadvantages. The tube, which often must be maintained in place for many weeks, may either become displaced or inadvertently removed quite early in the postoperative course. Occasionally, a decubitus ulcer of the larynx may result from its prolonged pressure. This complication is most unfortunate because it may result in either an edema of the glottis or a necrosis of the arytenoid cartilages. To avoid these various hazards and to assure alimentation during this critical period, we prefer a jejunostomy.

Case 5—History No 414414. A. I., age 57. Admitted October 1, 1937. Discharged November 2, 1937.

1931—Anterior gastro-enterostomy for duodenal ulcer.

1937—Disconnection of anterior gastro-enterostomy for healed jejunal ulcer, and posterior retrocolic gastro-enterostomy for gastric ulcer, with pylorospasm.

This patient has had abdominal pain since 1917. In 1931, he was operated upon for a duodenal ulcer. The extensive adhesions about the pylorus and duodenum prevented a radical operation, so that an anterior gastro-enterostomy was performed. He remained perfectly well until six months before admission, when he complained of epigastric pain and vomiting. He had a definite gastric retention at that time, which subsided following

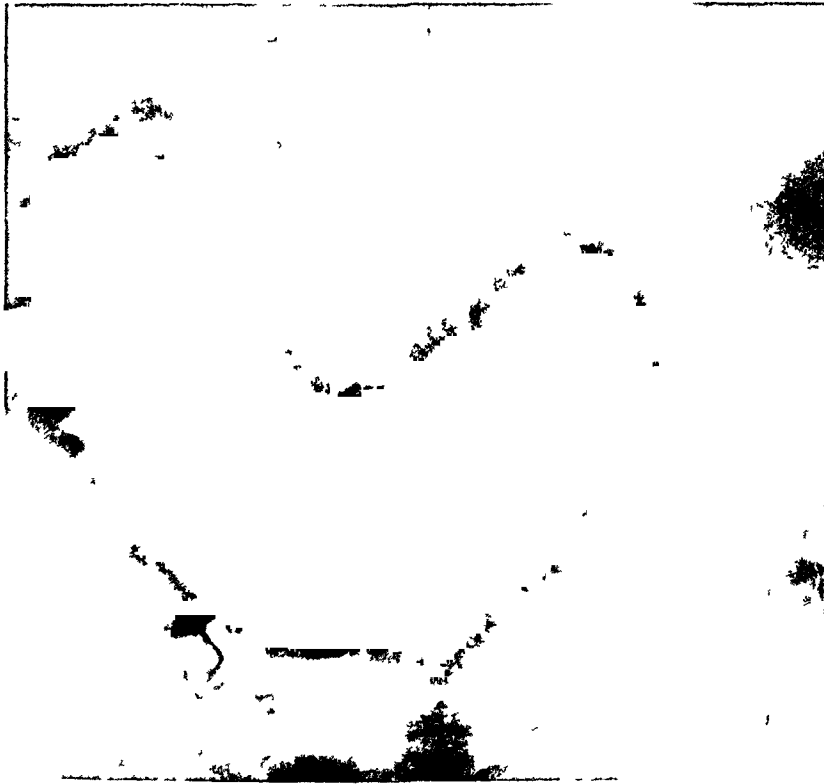
GASTROJEJUNAL ULCERATION

daily lavages One month before the second admission, the pain recurred, and for the past week he vomited after every meal He lost about eight pounds

Physical examination revealed a very anemic and emaciated individual There was a scar of a previous median incision Peristaltic waves were present in the left upper quadrant, passing laterally toward the center of the abdomen Hemoglobin 45 per cent Blood urea 20 mg , blood chlorides 500 mg , carbon dioxide 62 vol per cent The gastrointestinal series revealed a penetrating ulcer on the lesser curvature of the stomach, without marked pyloric obstruction There was, however, an 80 per cent six-hour residue There was no evidence of a patent gastro-enterostomy, but evidence of a jejunal ulcer The Rehfuess test meal showed a free hydrochloric acid of 46 units

Preoperatively, the patient was lavaged twice a day He improved so markedly that his complaints almost subsided, and the residue dropped to zero

On October 25, 1937, he was explored, under avertin and ethylene anesthesia The stomach was fish-hook in appearance and was dilated to three times normal size The stoma of the anterior gastro-enterostomy was contracted, and the site of a healed marginal ulcer Below this, there was evidence of a previous entero-enterostomy The previous gastro-enterostomy was separated without difficulty The gastric opening was sutured The jejunal orifice was used in the performance of a typical retrocolic gastro-



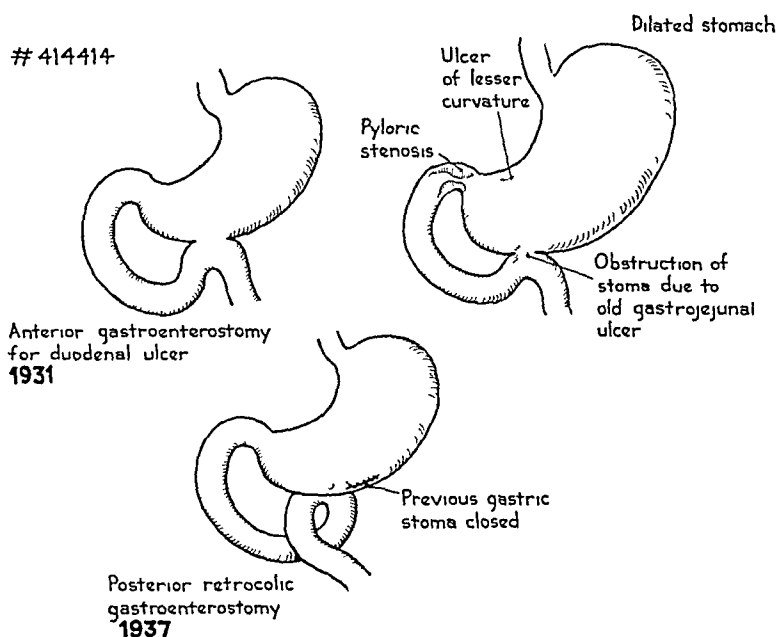
CASE 5—Roentgenogram illustrating an almost complete obstruction of the gastroenteric stomach

enterostomy The patient did perfectly well and, with the aid of three transfusions, had a normal convalescence He was discharged on the thirteenth day

Patient has been seen repeatedly, and when last seen, October 23, 1940, he weighed 159 pounds, and looked quite well He had no specific complaints, and no vomiting

(5) *Treatment of Resectable Gastrojejunal Ulcers Following Partial Gastrectomy*—In the majority, the recurrent ulceration may be ascribed in part to the persistence of free hydrochloric acid, due most likely to an inade-

quate removal of the antrum, which was performed either purposefully or inadvertently. Some surgeons practice a minimum partial gastrectomy as a matter of choice, others in the course of a Schmilnsky procedure (Case 6)



CASE 5—Schematic review of operative procedures

Case 6—History No 453947 A A, age 53 Admitted March 19, 1939 Discharged April 28, 1939

1934—Retrocolic posterior gastro-enterostomy for duodenal ulcer

1935—Schmilnsky operation for gastrojejunal ulcer

1939—Secondary radical subtotal gastrectomy, with antecolic terminolateral gastro-enterostomy and partial jejunectomy, with side-to-side jejunojejunostomy for multiple jejunal ulcers

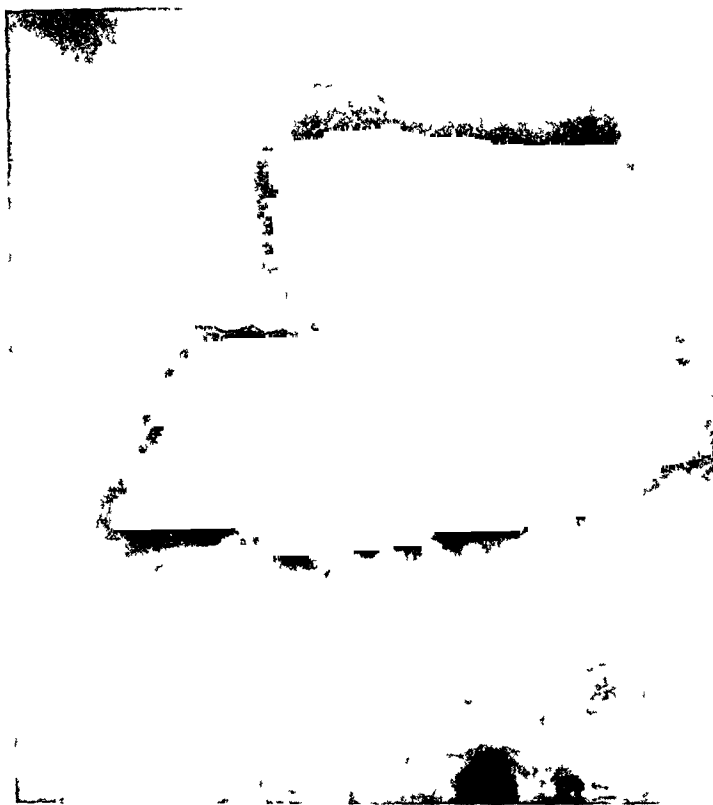
This is the first admission of a male, age 53, who was well until 13 years ago, when he developed preprandial pain, relieved by alkalis. Four years ago, a posterior retrocolic gastro-enterostomy was performed because of pain. He was improved after operation but noticed that, occasionally, the stools were tarry. One and one-half years ago he began to have episodes of epigastric pain accompanied by hematemesis. At this time, a diagnosis of gastrojejunal ulcer was made, and the Schmilnsky type of gastric and jejunal resection was performed. Following the operation, he bled profusely from the stomach, but this symptom gradually subsided until five months ago when severe epigastric pain recurred. During the month prior to admission he noted tarry stools.

Physical examination disclosed the fact that he was a well-developed, emaciated male, complaining of epigastric pain. There were two well-healed parallel scars in the right upper quadrant of the abdomen. Blood pressure 110/74, hemoglobin 75 per cent, blood chlorides 595 mg, CO₂ 61 vol per cent. Rehfuess test meal revealed a free acid of 90 units, total of 110. Stools were guaiac positive. A gastro-intestinal series showed a stomach upon which a partial resection had been performed. In the afferent jejunum, there was a constriction about one and one-half inches from the stoma, which was irregular. In the efferent loop, there was evidence of a penetrating jejunal ulcer. There was a delay in gastric emptying.

The patient was at first treated medically. In spite of almost constant milk drip,

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pain became so severe that operation was advised, and he was prepared with adequate doses of vitamins and desoxycorticosterone. On April 8, 1940, he was explored, under novocain field-block and cyclopropane anesthesia. There were omental adhesions to the anterior abdominal wall, and the resected stomach was bound to the under surface of the liver. It was normal in size. A healed jejunal ulcer was found at the jejunal site of the afferent loop as it entered the stomach and about one and one-half inches from this



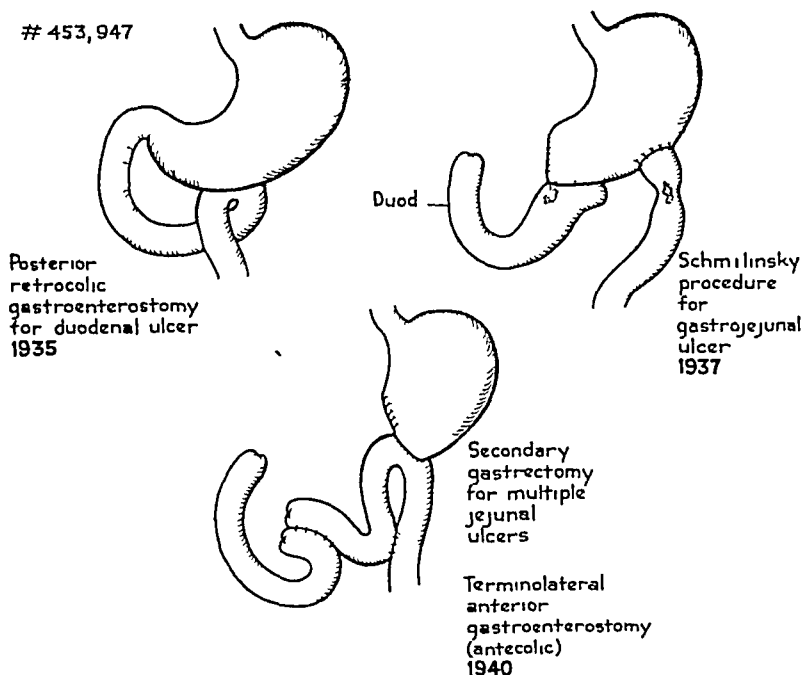
CASE 6—Roentgenogram showing Schmilinsky procedure, with ulcer of afferent and efferent jejunal loops

area was a slight constriction. A penetrating jejunal ulcer sealed-off by the transverse mesocolon was found in the efferent loop. Accordingly, both the jejunal loops were dissected free from the stomach. A partial resection of the jejunum which contained the ulcers was then performed, and the free openings were closed. Jejunal continuity was restored by a side-to-side jejunojejunostomy. A subtotal gastrectomy was then performed, removing 6 cm of the lesser curvature and 11 cm of the greater curvature, and an antecolic terminolateral gastrojejunostomy of the Hofmeister type was performed. Following the operation the patient did well, but his hemoglobin fell to 40 per cent, for which he received transfusions. The remainder of his course was complicated by a persistent gastric retention, which was treated by daily lavages and finally subsided. Wound healed and patient's symptoms were relieved. He was discharged on the seventeenth day.

When last seen, July 24, 1940, he had gained 50 pounds in weight. He was cautioned about the incessant use of tobacco.

In some of the recurrent cases in which a partial gastric resection followed a previous gastro-enterostomy, the surgeon left the previous gastro-enterostomy undisturbed, and simply removed that portion of the stomach which was distal to it. As a result a minimum resection was done (Case 7).

In all these cases in which a large gastric segment remains after a previous partial gastrectomy, the secondary gastrectomy must be more radical, provided that the gastrojejunal ulceration which is present is not so extensive



CASE 6—Schematic review of operative procedures

as to make the condition inoperable. If this condition existed, a preliminary jejunostomy was performed. The rationale of this procedure has been previously discussed.

Case 7—History No 423778 S I, age 48 Admitted May 25, 1938 Discharged June 7, 1938

1921—Excision of a duodenal ulcer, followed by gastro-enterostomy for pyloric obstruction

1935—Partial gastrectomy, with preservation of old posterior retrocolic gastro-enterostomy for bleeding duodenal ulcer

1938—Subtotal gastrectomy, with antecolic anterior Murphy button gastrojejunostomy, and entero-enterostomy for gastrojejunal ulcer

This patient had had an excision of a duodenal ulcer in 1921, followed three weeks later by a pyloric obstruction, for which a posterior retrocolic gastro-enterostomy was performed. In 1935, following three episodes of melena, which were thought to be due to gastrojejunal ulcer, he was explored, and it was the operator's impression at that time that the cause of the hemorrhage was a bleeding duodenal ulcer. Accordingly, a partial gastrectomy was performed, leaving the old gastro-enterostomy intact. Since the last operation, he has had innumerable severe attacks of bleeding, all of which were treated symptomatically on previous hospital admissions. On the day before his present entrance to the hospital, he developed mild abdominal cramps followed by the passage of tarry stools and some bright red blood.

Physical examination revealed a pale individual, with some epigastric tenderness on deep pressure. Hemoglobin 75 per cent, WBC 16,000, with 58 per cent polys, blood urea 20 mg, blood proteins 58 per cent. Following two transfusions, hemoglobin was

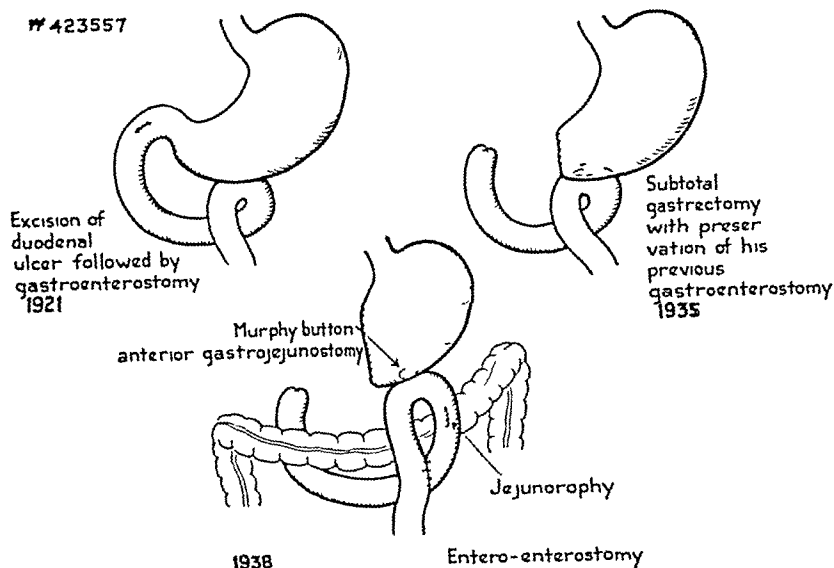
GASTROJEJUNAL ULCERATION

elevated to 80 per cent. Gastroscopy on two occasions revealed an ulcer on the gastric side of the posterior lip of the gastro-enteric stoma. Roentgenologic examination failed to reveal evidence of a gastrojejunal ulcer.

Operation was performed on May 26, 1938, under avertin and cyclopropane. The omentum was adherent to the previous scar, and the stomach was bound to the under



CASE 7—Roentgenograms taken in 1934 showing duodenal and gastrojejunal ulcers



CASE 7—Schematic review of operative procedures

surface of the liver by dense adhesions. The transverse colon was finally brought into the wound, exposing the site of a no-loop, anteperistaltic, posterior gastro-enterostomy. The afferent loop of this was constricted by adhesions. Definite induration was felt in the posterior region of the stoma, evidently the site of a healed marginal ulcer. A secondary subtotal gastrectomy was performed removing 6 cm of the lesser curvature and 13 cm of the greater curvature of the stomach. The proximal end of the small gastric segment was then closed, and an anterior antecolic button gastro-enterostomy, with a suture entero-enterostomy was performed. Prior to this the jejunal opening had been closed by a transverse jejunorrhaphy.

Patient's recovery was uneventful. When last seen, February 14, 1940, he had gained materially in weight, had no further episodes of bleeding, and seemed quite well.

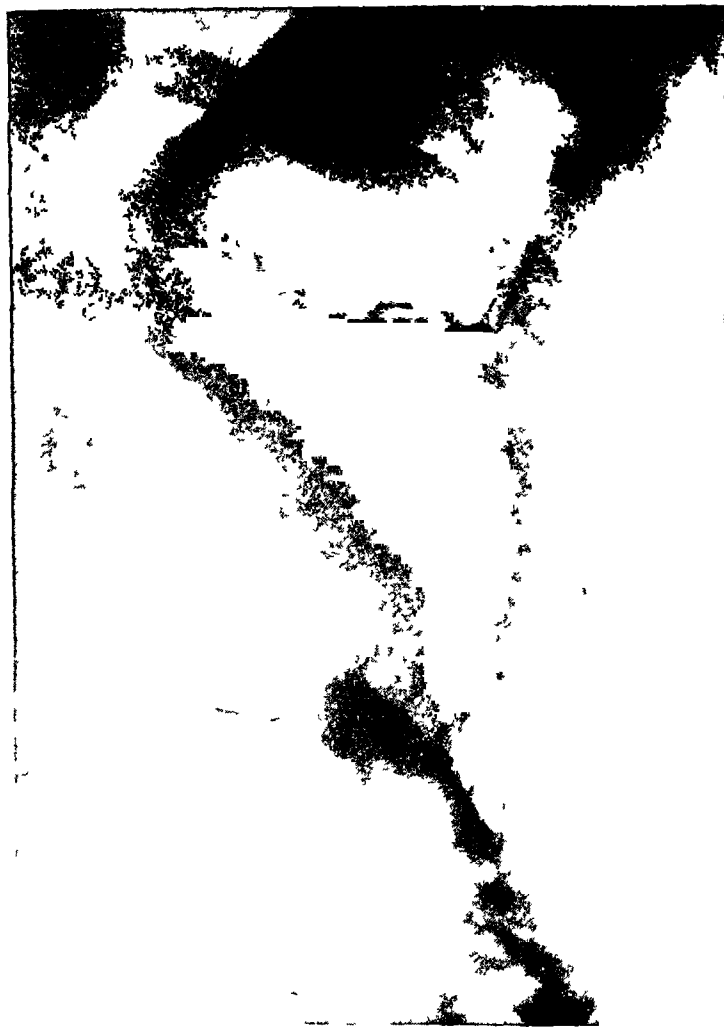
The removal of a gastric segment in a case of partial gastrectomy with a retrocolic anastomosis, complicated by gastrojejunal ulceration, is a difficult procedure. The mobilization of the ulcerated stoma from its attachment to the transverse colon, and occasionally the pancreas, must be carefully undertaken in order to avoid injury to the middle colic artery. A secondary radical subtotal gastrectomy of this type may, perforce, leave a segment of stomach so small that a suture gastro-enterostomy may be extremely difficult and often too time-consuming. In cases such as this, we have found the use of either the Murphy button or its modifications invaluable. The site of the jejunum chosen for the anastomosis, as a rule, was distal to the area of jejunal resection and its union to the stomach was made anterior to the colon. The button anastomosis was further secured by interrupted Lembert sutures. A button gastrojejunostomy in a high resection, as a rule, produced a sharp angulation between the afferent and efferent jejunal loops. In spite of the fact that a jejunojejunostomy in the average subtotal gastrectomy is obviously a poor procedure because it deprives the stomach of the beneficial effects of full duodenal regurgitation, we have employed it as a safety measure against a possible acute jejunal obstruction. Any obstruction involving the loop of bowel which has been recently sutured will invariably result in a dehiscence, with an ensuing fatal peritonitis.

(6) *Gastrojejunal Ulceration Following Radical Subtotal Gastrectomy*—Recurrent gastrojejunal ulcers following a radical subtotal gastrectomy of the Billroth II-type unfortunately occasionally occur. These patients represent an unfortunate group in which regardless of the extent of gastric resection, in spite of the full regurgitation of the duodenal contents, and the rapidity of the emptying, unneutralized free hydrochloric acid is still present in the remaining stomach. This, together with the constitutional tendency of the mucous membrane, especially of the jejunum, to ulcerate in the presence of free hydrochloric acid, produce a combination against which present-day surgery appears powerless. Theoretically, in order to cure this condition, total gastrectomy is indicated. The operation of total gastrectomy combined with jejunal resection results in a mortality of staggering proportions. As a matter of fact, in our hands, the attempt to remove additional portions of the stomach just short of a total gastrectomy gave an exceedingly high mortality. Therefore, when courses of medical treatment have proven to be ineffective, we have tried several palliative procedures in this type of case. Theoretically, with the chemical phase of gastric secretion eliminated by resection of the pylorus and antrum, the psychic phase of gastric secretion should be lessened by a vagotomy. Naturally, a vagotomy cannot be a complete one. In one case, in which a radical subtotal gastrectomy with exclusion was performed for massive duodenal ulceration, a gastrojejunal ulceration promptly took place. Inasmuch as this patient did not respond

to medical treatment, a transthoracic, bilateral supradiaphragmatic vagotomy was performed, dividing the main anterior and posterior vagus trunks, *ie*, about 60 per cent of the vagus nerve supply to the stomach. There was little reduction in acid values according to the insulin test meal, and very little improvement clinically (Case 8)

Case 8—History No 420331 K W, age 36 Admitted October 24, 1940 Discharged November 16, 1940

1938—Prepyloric exclusion for duodenal ulcer and subtotal gastrectomy, with Hofmeister retrocolic gastrojejunostomy



CASE 8—Roentgenogram showing jejunal ulcer following subtotal gastrectomy, with exclusion of duodenal ulcer

1939—Transthoracic bilateral vagotomy

1940—Thoracotomy for empyema

This is the readmission of a patient who, on a previous occasion, was treated medically for duodenal ulcer and who, because of intractability of pain in March, 1938, had a prepyloric exclusion of a massive penetrating duodenal ulcer and subtotal gastrectomy, with a Hofmeister retrocolic gastrojejunostomy, under spinal anesthesia

He was readmitted again, within two months after discharge, for a jejunal ulcer, verified roentgenologically. He was then referred to the genito-urinary clinic for medical treatment

In May, 1939, he was again admitted to the hospital for treatment, at which time he had a free acid of 40 and a total acidity of 48 units. Because of extreme loss of weight, and the intractability of his symptoms, due to the presence of a large gastrojejunal ulcer, a transthoracic, supradiaphragmatic, bilateral vagotomy was performed, November 18, 1939.

Postoperatively, he developed a pleural effusion, which was aspirated and found to be negative on culture. Pre- and postoperative insulin test meal for vagus function showed no essential difference.

On October 30, 1940, he was admitted to the service of Doctor Neuhof for an empyema thoracis, for which a thoracotomy, in the left paravertebral region, was performed. When last seen, December 17, 1940, the empyema cavity was rapidly closing, and the gastric symptoms seemed somewhat more under control.

In another case of massive jejunal ulceration following radical subtotal gastrectomy, an infradiaphragmatic, anterior vagotomy combined with a



CASE 9—Roentgenogram showing jejunal ulcer following subtotal gastrectomy for duodenal ulcer.

Stirling-type of procedure and a jejunostomy were performed. There was no reduction in the amount of free hydrochloric acid. The patient was, however, improved temporarily by a drip of amphogel. The present outlook in this type of case appears quite dismal (Case 9).

Case 9—History No 436115. L. R., age 44. Admitted October 21, 1940. Discharged February 9, 1941.

1939—Subtotal gastrectomy, with posterior retrocolic Murphy button gastrojejunostomy, for bleeding duodenal ulcer.

1940—Anterior vagotomy, Stirling procedure, and jejunostomy for gastrojejunal ulcer

A subtotal gastrectomy, with a posterior retrocolic Murphy button gastrojejunostomy was performed for a penetrating and bleeding duodenal ulcer in May, 1939, as an emergency procedure. The postoperative course was stormy and was complicated by an operative bronchopneumonia, a duodenal leak resulting in the formation of an intra-abdominal abscess, which was subsequently drained.

Patient was readmitted to the Medical Service on four separate occasions for recurrences of postprandial abdominal pain. In August, 1940, a gastro-intestinal series revealed a gastrojejunal ulcer. Because of the fact that this patient was not relieved by medical treatment, and had lost persistently in weight, he was reexplored, at which time a large gastrojejunal ulcer was found in the posterior wall of the gastrojejunostomy. The segment of stomach which remained was so small that no further resection was possible. Because of the marked ulceration in the jejunum, no jejunal resection was performed. Therefore, an anterior vagotomy and a Stirling-type of procedure were performed in the region of the cardia. A Witzel jejunostomy was done for alimentation. He developed a severe bilateral bronchopneumonia which almost caused his death. Although he was kept under observation for several months, there was no improvement clinically, despite the vagotomy, gastric mucin, injections of activin and paravertebral block of the nerve roots D9 and D10. The jejunal alimentation gave no relief. There was no clinical improvement in the condition of the patient. The insulin vagus test meals which were done pre- and postoperatively showed no difference. He was discharged finally to a convalescent home.

(7) *Gastrojejunocolic Fistulae*—One of the most serious complications of a jejunal ulcer is its penetration into the transverse colon. The fistula generally connects the efferent jejunal loop and the colon, and lies quite close to the gastro-enterostomy stoma. It is a condition requiring immediate surgical treatment to prevent rapid death from inanition. There have been many operations which have been devised for the surgical treatment of gastrojejunocolic fistula, depending upon the extent of the pathologic condition present at the time of operation. We are convinced that separation of the gastro-enterostomy, with or without colonic resection, is an inadequate procedure. The aim of any operation employed, therefore, should be the elimination of the jejunal ulcer by excision, the restoration of colonic continuity, and the performance, either simultaneously or eventually, of an adequate gastrectomy. In 1939, Pfeiffer² suggested a preliminary ascending colostomy with the function of a spur, insuring a complete diversion of the fecal current. He felt that the inflammatory exudate present about these lesions would be diminished by this procedure, making any subsequent surgery much simpler. Having seen the benefits of jejunostomy in diminishing the massive exudates about a gastrojejunal penetration, we were convinced of the logic of employing a preliminary colostomy in large gastrojejunocolic fistulae in patients in poor condition. In patients in which the lesion is not extensive, the operation may be performed either in one or two stages (Case 10).

Case 10—History No 426675 N W, age 49

1935—Retrocolic posterior gastro-enterostomy for duodenal ulcer with pyloric stenosis

1938—Ascending colostomy with spur for gastrojejunocolic fistula (May)

1938—Subtotal gastrectomy, with antecolic terminolateral gastrojejunostomy and jejunal resection, with jejunojejunostomy for jejunal ulcer (July)

1938—Closure of colostomy

This patient was first admitted to the hospital January 7, 1935. He gave a nine-year history of intermittent attacks of epigastric, postprandial burning pain associated with nausea, occasional vomiting, eructations, and pyrosis. One week before admission, a gastro-intestinal series was done, and a penetrating duodenal ulcer, with a large gastric residue after five hours, was found. On January 12, 1935, under spinal anesthesia, through a median epigastric incision, a retrocolic, posterior no-loop gastro-enterostomy was performed for chronic duodenal ulcer producing a partial pyloric obstruction. The postoperative course was uneventful, and he was discharged 12 days after operation. The patient felt fairly well until three months before his second admission, when he again began to have frequent bowel movements accompanied by the belching of fecal tasting gas. He had lost ten pounds during this period. Barium enema revealed the presence of a gastrojejunocolic fistula.

He was readmitted to the hospital April 13, 1938. He appeared to be well-nourished. He belched frequently, with a feculent odor apparent on the breath. There was a small incisional hernia at the previous operative site. Hemoglobin 70 per cent. Urine clear. Blood chemistry normal. Electrocardiogram negative. A night Reflux test meal revealed a free acid of 80, and a total acid of 128 units. When a methylene blue enema was administered to the patient, the dye appeared 20 minutes later through a gastric Levin tube, establishing the presence of a gastrojejunocolic fistula. On May 6, 1938, under spinal anesthesia, and through an upper right rectus muscle-splitting incision, the ascending colon was mobilized. Crushing clamps were applied to the midportion of the colon, which was exteriorized, while the distal and proximal limbs were united to form a spur. The colon was divided between the clamps. The proximal colonic loop was opened 24 hours after operation, and the clamps were removed on the sixth day. Almost immediately, the patient noted that his breath was no longer fecal. At the time of discharge, the entire fecal stream was side-tracked and draining well through the proximal colostomy. The distal colonic segment, however, was still in communication with the stomach, as was evidenced by the appearance of methylene blue in the gastric Levin tube 20 minutes after the dye had been administered in an enema. He was discharged May 17, 1938.

The patient reentered the hospital July 8, 1938. He was asymptomatic and had gained about 18 pounds. A gastro-intestinal series showed evidence of a previous gastro-enterostomy. The barium mixture passed through the stoma which was tender and irregular, within the jejunum about two inches from the stoma, a large ulcer pocket, one inch in diameter was observed. There was no evidence of a gastrojejunocolic fistula. A barium enema, injected through the colostomy, showed irregularity of the midportion of the transverse colon but no communication between the colon and stomach. On July 16, 1938, under anesthesia, the scar of the previous median epigastric incision was excised. In the region of the previous gastro-enterostomy there was a hard, inflammatory mass about the size of a lemon, which included the stomach, colon, and jejunum. About 12 inches from the duodenojejunal angle, the efferent jejunum was found to be the seat of a definite ulceration almost opposite the neostomy. The fistula in the colon had evidently healed and was replaced by hard, fibrous, indurated connective tissue. The stomach itself was dilated to about twice its normal size, and this was apparently caused by a stenosis at the duodenum due to a healed duodenal ulcer. A partial jejunectomy, with end-to-end jejunojejunostomy, for a jejunal ulcer, and a subtotal gastrectomy with a Hofmeister antecolic gastro-enterostomy, for healed ulcer of the duodenum, with pyloric stenosis, was performed.

After a moderate febrile reaction, and some gastric regurgitation, the patient did well. A spur-crusher was applied to the colostomy two weeks after operation, and two weeks later, an extraperitoneal closure of the colostomy was performed, under ethylene,

GASTROJEJUNAL ULCERATION

by Dr P Klingenstein When last seen, March 1, 1941, the patient looked and felt well
He had gained 25 pounds since his operation

SUMMARY

The pathology, symptomatology, physical, roentgenographic, gastrosopic, and chemical findings in cases of gastrojejunal ulceration following gastro-enterostomy, partial, and subtotal gastrectomy are reviewed The medical treatment and surgical indications are discussed

The surgical management of gastrojejunal ulceration and its complications depend upon the pathology present at the time of operation Cases are arbitrarily divided into (1) Perforation of acute gastrojejunal ulcers following gastro-enterostomy, (2) resectable gastrojejunal ulcers following gastro-enterostomy, (3) massive gastrojejunal ulcers following gastro-enterostomy, (4) cicatrized gastrojejunal ulcers following gastro-enterostomy, (5) resectable gastrojejunal ulcers following partial gastrectomy, (6) resectable gastrojejunal ulcers following subtotal gastrectomy, and (7) gastrojejunocolic fistula

A detailed discussion of the surgical problems involved in each group with case presentations are given

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¹ Berg, A A ANNALS OF SURGERY, 92, 340, September, 1930

² Pfeiffer, D B, and Kent, E M ANNALS OF SURGERY, 110, 659, October, 1939

SURGICAL MANAGEMENT OF CARCINOMA OF THE AMPULLA OF VATER AND OF THE PERIAMPULLARY PORTION OF THE DUODENUM*

VERNE C HUNT, M D

LOS ANGELES, CALIF

IN 1935, Whipple, Paisons, and Mullins presented a paper before this Association in which they directed attention to the problems involved in the surgical treatment of carcinoma of the ampulla of Vater and of the periampullary portion of the duodenum. They described and illustrated a surgical procedure performed in two stages which embraces the fundamental principles of cancer surgery in general, *i e*, the excision of tissue *en bloc*, wide of the growth, which stimulated anew an endeavor to surgically extirpate neoplastic disease in that situation.

Characteristically, patients in whom neoplastic obstruction of the terminal portion of the common duct occurs, lose weight rapidly through retention of bile and the loss of external pancreatic secretion, to become subjects for surgical procedures in which the risk of operation is far greater than in operations employed for the relief of temporary, intermittent, or incomplete obstruction of the common duct resulting from benign disease. Even though the advantages of drainage and decompression of the biliary tract preliminary to any radical surgical procedure for the extirpation of neoplastic disease in the ampullary region have long been recognized the risk of such operations has in the past been great (30 to 70 per cent).

Since 1898, when Halsted successfully performed the first radical operation for carcinoma of the ampulla of Vater through resection of the duodenum with end-to-end anastomosis and reimplantation of the common and pancreatic ducts into the duodenum, less than 125 instances have been recorded in which radical excision of malignant disease in this situation has been accomplished. Should one rely solely upon the number of cases in which surgical extirpation of a malignant lesion in the periampullary region has been undertaken, he would be inclined to the opinion that malignant disease in this situation is exceedingly uncommon. In searching the literature for recorded instances of surgical excision and radical resection of neoplastic disease in the ampullary region, a startling number of cases were encountered in which the diagnosis was made at necropsy, which more often than not disclosed an entirely localized operable lesion. In 1913, Outerbridge collected 110 cases of carcinoma of the ampulla of Vater and in only 22 of those had a resection of the ampulla been performed. In 1939, Lieber, Stewart, and Lund collected 399 cases of carcinoma of the ampulla of Vater which, with the exception of a few cases that were not available to them, represented all of the cases reported in the literature.

*Read before the American Surgical Association, White Sulphur Springs, W Va, April 28-30, 1941.

Upcott, Pallin, Einhorn and Stetten, Busch, Fulde, Muller and Rodemaker, among others, have presented extensive reviews of this subject. In 1927, however, Cohen and Colp provided the most complete collection of 58 cases in which radical operation for carcinoma of the ampulla of Vater had been performed during the period from 1898 to 1925. In 1934, reporting a case which had been successfully operated upon, Hunt and Budd collected 17 additional cases, which added to those of Cohen and Colp, provided a collective review of 76 cases. In 1935, Whipple, Parsons, and Mullins reported three cases of their own and added 19 cases from the literature since the report of Cohen and Colp. In a late collective review by Kafka, 115 cases are listed in which operation had been performed. I have recently collected from the literature and through personal communication 32 cases (abstracts appended) which, with those here recorded and added to those collected by Cohen and Colp, Whipple, Parsons and Mullins, and Hunt and Budd, provide 124 cases for review (Table I).

Four cases are herewith reported in which radical operation was successfully performed for carcinoma of the ampulla of Vater and periampullary region of the duodenum. Case 1 was reported before the Western Surgical Association in December, 1934, and was recorded in *Surgery, Gynecology, and Obstetrics* in November, 1935. The case is here presented in abstract form in order that the subsequent course, ultimate result, and necropsy findings may be made a matter of record.

CASE REPORTS

Case 1—St Vincent's Hospital, No 3047-34. A woman, age 54, on August 15, 1934, gave a history of epigastric distress of three weeks' duration, with progressive jaundice. There had never been any acute pain or chills, but there had been a daily temperature of 100° F. A weight loss of ten pounds had occurred. At the time of examination, the patient was poorly nourished, weighed 98 pounds and was deeply jaundiced. General physical examination was essentially negative except for the presence of a large cystic mass occupying the entire upper left quadrant of the abdomen, which, upon subsequent investigation, proved to be a huge hydronephrotic left kidney. Apart from a secondary anemia, laboratory data, as detailed in a previous report, were essentially negative. A preoperative diagnosis of obstructive jaundice, probably due to carcinoma of the head of the pancreas was made.

Operation—(Hunt) August 17, 1934. Transduodenal cautery excision of the ampulla of Vater with reimplantation of the common duct and duct of Wirsung into the posterior wall of the duodenum and external drainage of the common duct. The gallbladder was greatly distended and the common duct was dilated to about 2.5 cm in diameter, and both of these structures contained colorless, mucoid material under pressure. An incision in the anterior wall of the duodenum exposed a nonulcerating tumor of the ampulla, projecting into the lumen of the duodenum (Fig 1). A wide transduodenal cautery excision of the tumor was made, dividing the dilated common and pancreatic ducts (Figs 2 and 3). The mesial edges of the common duct and the duct of Wirsung were sutured together and the circumferential edge of each duct was sutured to the mucosa of the posterior wall of the duodenum (Fig 4). Temporary external drainage of the common duct was established by an ordinary catheter. *Pathologic Diagnosis*. Papillary adenocarcinoma primary in the ampulla of Vater, Grade III (Fig 5).

TABLE I

124 CASES OF RADICAL OPERATION FOR CARCINOMA OF THE PERIAMPULLARY REGION OF THE DUODENUM
FROM 1898 TO 1941

Year	Surgeon	Sex	Age	Operation	Result
1898	Halsted*	M	60	Resection of duodenum (circular suture) (end to end) reimplantation of choledochus and pancreatic ducts and cholecystostomy	Death 7 mos after resection from recurrence
1899	Riedel*	F	50	Transduodenal excision	Died from operative shock same day
1900	W J Mayo*	F	59	Cholecystostomy 3 mos later transduodenal excision with the cautery 18 mos later cholecystoduodenostomy because of recurrence	Died after operation for recurrence from shock
1901	Czerny*	M	66	Transduodenal excision and cholecystostomy	Died after 5 days from retroduodenal phlegmon
1901	Rivford*	F	33	Cholecystostomy and 1 mo later transduodenal excision 8 mos later cholecysto-enterostomy because of recurrence	Died 4 mos after the last operation from recurrence
1903	Koerte*	F	44	Transduodenal excision and choledochopancreaticoduodenostomy Drainage of hepatic and pancreatic ducts and gallbladder	Died 8 days after operation
1904	Mayo Robson*	M	33	Resection of duodenum and pylorus, suture of duodenum and pylorus, cholecystostomy	Died few days after operation
1904	Koerte*	F	53	Transduodenal plastic on papilla (excision of stricture) Drainage of pancreatic and hepatic ducts and cholecystostomy 1 1/4 yrs later resection of duodenum (circular and end to end suture) common and pancreatic ducts cut through sutured together and reimplanted into posterior duodenal wall	Operative recovery Patient well for 1 1/2 yrs, then jaundice returned Died third day after operation
1904	Arnsperger*	F	43	Transduodenal excision and insertion of choledochus Drainage of hepatic duct	Died 2 days after operation from hemorrhage
1905	Koerte*	F	47	Transduodenal excision and common duct reimplanted into duodenum	Operative recovery Alive 22 yrs after operation
1905	Vertroogen*	F	33	Transduodenal excision	Died 11 days after operation from hematemesis and duodenal leakage
1905	Cordua*	F	41	Transduodenal excision, Cholecystectomy and gastro enterostomy	Operative recovery Died 1 yr later from recurrence
1905	Mayo*	M	49	Retroduodenal papillectomy choledochoduodenostomy	Died after 8 wks
1908	Morrin*	F	42	Transduodenal excision cholecystojejunostomy	Operative recovery Died 2 1/2 yrs later from recurrence
1908	Cuneo*	M	59	Transduodenal excision reinsertion of choledochus gastro enterostomy	Died 4 days after operation
1908	Navarro*	M	60	Transduodenal excision reinsertion of choledochus and pancreatcus	Operative recovery Alive 2 yrs after operation No recurrence
1909	Kausch*	M	49	Cholecystojejunostomy 2 mos later resection of duodenum and part of pancreas Pancreaticoduodenostomy and gastro enterostomy	Operative recovery Died 3/4 yr later from cholangitis
1910	Stein*	?	?	Duodenotomy Soft friable papillary mass surrounding papilla cut-retted away	Operative recovery Patient alive 7 mos later

* Collected by Cohen and Colp in 1927

PERIAMPULLARY CARCINOMA

TABLE I (Continued)

Year	Surgeon	Sex	Age	Operation	Result
1910	Kraske*	F	60	Transduodenal excision of choledochus	Reinsertion Operative recovery Severe hemorrhage first day postoperative After 23 mos developed slight jaundice probably from a recurrence
1910	Kelly*	F	45	Transduodenal excision	Reimplantation of choledochus Operative recovery Patient alive 9 yrs after operation
1910	Kerr	M	52	Transduodenal excision with reimplantation common duct and duct of Wirsung	Lived 3 yrs (Kafka)
1911	Hotz*	F	61	Retroduodenal excision and gastroenterostomy	Operative recovery
1911	Slaymer*	M	48	Retroduodenal excision reinsertion of choledochus and pancreatic Choledochostomy and jejunostomy	Died after 3 days from cholemic hemorrhages
1912	Hartman*	?	?	Transduodenal excision with reimplantation of choledochus	Operative recovery Recurrence 2 mos after operation
1912	Upcott*	M	65	Transduodenal excision and reinsertion of choledochus Cholecystostomy	Operative recovery Treated later with radium because nodes suspected of being malignant were not removed
1912	Oppenheimer*	F	63	Choledochotomy at first then resection of entire choledochus and surrounding indurated area Hepatic duct sutured to duodenum Cholecystectomy Stump of pancreatic duct which had been cut through sunk into duodenal wall	Operative recovery Died 1 yr later from recurrence in liver
1913	Hirschel*	F	47	Circular resection of the duodenum End-to-end suture Choledochoduodenostomy with tube Resection of part of pancreas and pancreaticoduodenostomy and gastroenterostomy	Operative recovery Died 1 yr later from recurrence
1913	Alglave*	?	?	Transduodenal excision Choledochostomy	Died 8 days after operation from cholemia and anuria
1913	Hartman*	?	?	Transduodenal excision Reimplantation of choledochus	Operative recovery Patient alive 18 mos after operation
1913	Clermont*	?	?	Transduodenal excision	Died night of operation from hemorrhage
1913	Kleinschmidt*	F	51	Cholecystectomy Transduodenal excision	Died eighth day from peritonitis
1914	Docq-VanPsever*	?	?	Transduodenal excision	Operative recovery
1914	Docq-VanPsever*	?	?	Transduodenal excision	Died fourth day from hemorrhage
1914	Wiede*	?	?	Transduodenal excision	Operative recovery
1914	Wiede*	?	?	Transduodenal excision	Died from cholemic hemorrhages At postmortem no metastases found
1916	Akerblom*	F	72	Transduodenal excision	Died after 8 days from cholemic hemorrhages
1917	Akerblom*	?	?	Transduodenal excision	Died after 2 days from pancreatic hemorrhage

* Collected by Cohen and Colp in 1927

|| Collected by Hunt in 1941

TABLE I (Continued)

Year	Surgeon	Sex	Age	Operation	Result
1918	Anschutz*	F	36	Transduodenal excision and reimplantation of choledochus Pylorus occluded and posterior gastro enterostomy Cholecystostomy for 8 days	Operative recovery Gained 30 lbs in 4 mos
1919	Lundblad*	F	59	Transduodenal excision	Died after 3 days from cholemic hemorrhages
1919	Olani*	"	"	Transduodenal excision and reimplantation of choledochus Cholecystectomy with drainage	Operative recovery Patient alive 4 yrs later
1919	Arnsperger*	F	50	Transduodenal excision and reimplantation of choledochus Hepatic drainage	Operative recovery Patient died 6 mos later from metastases
1919	Schussler	M	43	Resection of duodenum with reimplantation of common duct and duct of Wirsung	Death ninth day from hemorrhage
1919	Schussler	F	34	Transduodenal excision and reimplantation of common duct	Recovery Good health at end of 4 mos
1920	Blad	F	62	Transduodenal excision and reimplantation of common duct	Recovery Good health at end of 16 mos
1920	Brentano*	M	45	Transduodenal excision	Operative recovery Nine mos later local recurrence
1921	Propping*	F	17	Transduodenal excision and reimplantation of pancreatic and choledochus ducts	Operative recovery Alive 1 yr later and gained 30 lbs
1921	Kleinschmidt*	F	41	Transduodenal excision Drainage of duct of Wirsung	Operative recovery Well 7 mos later
1922	Renshaw*	"	"	Choledochotomy transduodenal excision (knife and cautery) cholecystoduodenostomy	Died 9 days after operation
1922	Bruett*	F	59	Cholecystectomy Transduodenal excision and reimplantation of choledochus and duct of Wirsung	Died 2 days after operation from peritonitis
1922	Bruett*	M	50	Transduodenal excision and reimplantation of choledochus and duct of Wirsung	Operative recovery Died 1/4 yr later
1922	Bruett*	M	43	Transduodenal excision and reimplantation of choledochus and pancreatic duct	Operative recovery Alive 6 mos later
1922	Tenani*	"	"	First operation Duodenotomy posterior gastro enterostomy, division of choledochus with implantation of proximal end into efferent duodenal segment Suture of duodenum and closure of abdomen without drainage Second operation (one mo later) Duodenum mobilized and descending part resected Diseased head of pancreas removed and pancreatic stump sutured into efferent duodenal segment and suture line protected with peritoneum	Postoperative reaction severe Patient free from recurrence 3 yrs after operation
1922	Judd†	M	55	First stage Cholecystostomy Second stage Transduodenal excision and choledochoduodenostomy	Death 2 days after operation
1923	Dalla Valle*	"	"	Transduodenal excision and reimplantation of choledochus	Died 3 days after operation

* Collected by Cohen and Colp in 1927

|| Collected by Hunt in 1941

PERIAMPULLARY CARCINOMA

TABLE I (Continued)

Year	Surgeon	Sex	Age	Operation	Result
1923	Pozzi*	?	?	Duodenotomy Excision of papilla with reimplantation of duct of Wirsung and choledochus Cholecystogastrostomy	Operative recovery
1923	Pozzi*	?	?	Choledochotomy Transduodenal excision of papilla with reimplantation of choledochus and Wirsung Cholecystogastrostomy	Died 6 days after operation from peritonitis
1923	Pozzi*	?	?	Duodenotomy Excision of papilla with reimplantation of choledochus and duct of Wirsung	Operative recovery Patient alive 3 yrs after operation
1923	Beer*	M	34	Transduodenal excision Cholecystogastrostomy	Died in 10 hrs from shock
1924	Moschcowitz*	F	54	Choledochotomy Transduodenal excision Drainage to suture lines of common duct and duodenum	Died 5 days after operation from hemorrhage
1924	Tomaschewitch*	?	?	Transduodenal excision	Death 11 days after operation from duodenal fistula
1924	Brenner	M	58	Transduodenal excision	Recovery Subsequent course?
1925	Gohrbrandt*	M	?	Transduodenal excision and reimplantation of common bile and pancreatic ducts	Operative recovery Alive 4 mos later
1925	Muller*	M	52	Transduodenal excision	Operative recovery Death from metastases 4 yrs and 8 mos after operation
1925	Cohen*	F	44	Choledochotomy Transduodenal excision Cholecystostomy and drainage	Operative recovery Died 11 mos later from metastases
1925	Hansen†	M	44	One stage transduodenal excision and cholecystostomy	Operative recovery Recurrence and death in 18 mos
1925	Konjetzny†	M	55	One stage combined retroduodenal and transduodenal excision, reimplantation of common duct and duct of Wirsung	Recovery
1925	Homans‡	?	?	One stage transduodenal cautery excision	Well after several years
1925	Cabot††	M	35	One stage transduodenal excision and reimplantation of common duct	Well after 8 yrs
1926	Eiselsberg	?	?	Transduodenal excision	Recovery Subsequent course?
1926	Eiselsberg	?	?	Transduodenal excision	Death third day from hemorrhage
1926	Lagos and Dominguez	M	41	Transduodenal excision and reimplantation of common duct	Death 16 hrs after operation, hemorrhage
1927	Clar††	?	?	One stage transduodenal excision with reimplantation of common duct and the duct of Wirsung	Living and well 5 yrs after operation
1927	Fulde††	M	46	One stage transduodenal excision with reimplantation of common duct and the duct of Wirsung	Living and well 2 yrs after operation
1928	Coller††	M	64	One-stage transduodenal excision with reimplantation of common duct	Death on fourth day (cholema)
1928	Busch††	M	53	First stage Cholecystostomy Second stage Transduodenal excision with reimplantation of common duct and duct of Wirsung	Well after 1 yr

* Collected by Cohen and Colp in 1927

† Collected by Hunt in 1934

‡ Collected by Whipple Parsons and Mullins in 1935

|| Collected by Hunt in 1941

TABLL I (Continued)

Year	Surgeon	Sex	Age	Operation	Result
1928	Llambias†	M	42	One stage transduodenal excision with reimplantation of the common duct and duct of Wirsung, cholecystectomy and choledochostomy	Recovery
1928	Del Valle‡	M	42	One stage transduodenal excision, cholecystectomy and choledochostomy	Recovery
1929	Klinkert‡	M	53	First stage Cholecystojejunostomy Second stage Transduodenal excision and gastro enterostomy	Operative recovery Death in 3 mos from liver metastases
	Pollet‡	?	?	First stage Cholecystojejunostomy Second stage Transduodenal excision with reimplantation of common duct and duct of Wirsung	Recovery
1929	Denks†	F	31	One stage resection of duodenum and part of head of pancreas, end to end anastomosis of duodenum to pylorus, reimplantation of common duct into stomach	Death on third day No metastases at autopsy
1929	Denks†	M	?	One stage transduodenal excision and reimplantation of common duct and duct of Wirsung, choledochostomy	Death on sixth day
1930	Bengoler‡	F	37	One stage excision through choledochotomy opening and choledochostomy	Recovery Secondary operation 3 mos later from recurring jaundice, metastases
1931	Walters††	M	50	One stage transduodenal excision with reimplantation of common duct into duodenum	Operative recovery
1931	Pemberton††	M	44	One stage transduodenal excision with reimplantation of pancreatic duct into duodenum, choledochoduodenostomy	Recurrence and death 2 yrs after operation
1931	De Beule	?	?	Transduodenal excision and reimplantation of common duct	Recovery Metastases to liver within few mos
1931	De Beule	?	?	Transduodenal excision and reimplantation of common duct	Lived 3 yrs, death from influenza
1931	De Beule	?	?	Resection of duodenum and end-to-end anastomosis of duodenum, cholecystogastrostomy	Death soon after operation
1932	Judd††	M	38	First stage Cholecystostomy and choledochostomy Second stage 1 mo later transduodenal excision	Recurrence 9 mos after operation requiring cholecystogastrostomy 7 mos later gastro enterostomy, lived 2½ yrs
1933	Potter††	F	57	One stage transduodenal excision with reimplantation of common duct and the duct of Wirsung	Operative recovery Death 6 mos later, metastases?
1933	Lauwers††	M	51	One stage transduodenal cautery excision and cholecystojejunostomy	Living and well 3 yrs 10 mos after operation
1933	Lauwers††	M	52	One stage transduodenal excision with reimplantation of duct of Wirsung, cholecystojejunostomy	Well 9 mos after operation
1934	Snyder and Lium	M	48	First stage Cholecystoduodenostomy and drainage of common duct Second stage Transduodenal excision, with reimplantation duct of Wirsung and external catheter drainage of duct of Wirsung	Recovery Subsequent course?

† Collected by Hunt in 1934

‡ Collected by Whipple, Parsons and Mullins in 1935

|| Collected by Hunt in 1941

PERIAMPULLARY CARCINOMA

TABLE I (Continued)

Year	Surgeon	Sex	Age	Operation	Result
1934	Santero†	M	50	One stage transduodenal excision	Recurrence 17 mos after operation Second radical excision at this time Death 22 mos after first excision
1934	Santero†	F	72	One-stage transduodenal excision	Recurrence 4 mos later necessitating palliative operation Death 19 mos after first operation
1934	Hunt† (Case 1)	F	54	One stage transduodenal excision, with reimplantation of common duct and the duct of Wirsung, choledochostomy	Lived 25 mos, death from retroperitoneal mediastinal metastases
1935	Whipple‡	F	60	First stage Cholecystostomy and choledochoduodenostomy Second stage Transduodenal excision and excision of part of head of the pancreas with pancreaticoduodenostomy	Death 36 hrs after operation from duodenal leakage
1935	Parsons‡	M	53	First stage Cholecystogastrostomy Second stage Resection of duodenum and head of pancreas with closure of pancreatic stump, end-to-end anastomosis of duodenum Third operation 8 days later Anterior gastro enterostomy and entero enterostomy	Death in 8 mos of cholangitis
1935	Whipple‡	M	49	First stage Gastro enterostomy ligation and division of common duct, and cholecystogastrostomy Second stage Resection of duodenum and head of pancreas with closure of pancreatic stump	Recovery Death after 28 mos of metastases to liver
1935	Janes‡	M	?	First stage Cholecystogastrostomy Second stage (3 wks later) Resection duodenum and adjacent pancreas, closure pancreatic stump, ligation of common duct, and gastro enterostomy	Death fifth postoperative day of pneumonia
1935	Kafka	M	52	Transduodenal excision and reimplantation of common duct and duct of Wirsung	Well 22 mos after operation Death of unknown cause 2 yrs after operation
1935	Nemeny	M	42	Resection of duodenum and part of head of pancreas, pancreaticoduodenostomy, pylorojejunostomy and jejunojejunostomy	Well at end 16 mos having regained nearly all weight
1936	Bumm (Geisthovel)	M	54	Transduodenal excision and reimplantation of common duct and duct of Wirsung, cholecystoduodenostomy	Six mos after operation well and gained 22 lbs
1936	Orator	F	48	Whipple operation first-stage, cholecystogastrostomy and posterior gastro enterostomy Second stage Resection of duodenum and part of head of the pancreas	Pancreatic fistula 3 mos after operation jejunostomy was provided to receive external pancreatic fistula
1936	Hyde and Young	F	76	Transduodenal excision and reimplantation of common duct and duct of Wirsung, choledochostomy	Well at end of 3 yrs

† Collected by Hunt in 1934

‡ Collected by Whipple Parsons and Mullins in 1935

|| Collected by Hunt in 1941

TABLE I (Continued)

Year	Surgeon	Sex	Age	Operation	Result
1936	Hollenberg§	F	45	Two stage radical operation of resection of the duodenum and head of the pancreas	Pancreatic fistula persisted for 8 to 9 mos. Following spontaneous closure of fistula excellent health for 1½ yrs. Death of local recurrence 34 mos after resection
1937	Hoffman and Pack	M	58	First operation T tube drainage of common duct Second operation Transduodenal excision	Death 6 hrs after operation from hemorrhage
1937	Mallet Guy	F	56	Transduodenal excision and choledochostomy	Recovery Subsequent course?
1937	McCabe	M	67	Transduodenal excision and reimplantation of common duct and duct of Wirsung, choledochostomy	Recovery after postoperative hemorrhage Subsequent course?
1937	Brunschwig	F	41	Transduodenal excision and reimplantation of common duct and duct of Wirsung	General condition good after 15 mos
1937	Roscher	M	55	First stage Cholecystogastrostomy Second stage Resection of duodenum and part of head of pancreas division and ligation common duct implantation of common duct into jejunum, posterior gastro enterostomy	Lived 5 mos. Death due to bronchopneumonia metastases?
1937	Divis	F	65	One stage transduodenal excision with reimplantation of common duct and duct of Wirsung, choledochoduodenostomy	Lived 1 yr, cardiac death
	Janes§	?	?	Two stage radical operation of resection of the duodenum and head of the pancreas	Death 2 wks after operation from massive hemorrhage
	Schullinger§	?	?	Two stage radical operation of resection of the duodenum and head of the pancreas	Death 2 wks after resection of pneumonia
1938	Trout	M	55	Whipple operation in one stage cholecystojejunostomy, posterior gastro enterostomy, division and ligation of common duct, resection of duodenum and part of head of pancreas <i>en bloc</i>	Death within a few hours after operation
1938	McNeely (McNeely River and Rapina)	F	63	Transduodenal excision and reimplantation of common duct and duct of Wirsung	Recovered Jaundice recurred in 16 mos due to stricture at site of implantation, cholecystogastrostomy then performed Living and well 26 mos after excision of tumor
1939	River	M	55	Transduodenal excision and reimplantation of common duct, duct of Wirsung not seen	Jaundice recurred in 8 mos due to stricture site of implantation, cholecystojejunostomy Recovery Well 9 mos after operation
1939	River	M	55	Transduodenal excision and reimplantation of common duct and duct of Wirsung, cholecystostomy	Well 9 mos after operation
1940	Maddock	M	36	Resection of duodenum and end to end anastomosis of duodenum reimplantation of common duct, cholecystectomy	Death on 14th day of peritonitis

|| Collected by Hunt in 1941

§ Collected by Whipple in 1938

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TABLE I (Continued)

Year	Surgeon	Sex	Age	Operation	Result
1940	Orr	M	47	Whipple operation First stage Choledochogastrostomy and posterior gastro enterostomy Second stage Division and ligation of common duct resection of duodenum and part of head of the pancreas	Recovery Small pancreatic fistula persisting 7 mos after operation
1941	Ransom	M	2	First stage Cholecystojejunostomy jejunojejunostomy, posterior gastro enterostomy Second stage Resection of duodenum and part of head of the pancreas, ligation of common duct and duct of Wirsung	Recovery Pancreatic fistula developed but was nearly closed on 25th postoperative day
1941	Whipple	M	58	Two-stage operation, Whipple radical resection of duodenum and part of head of the pancreas	Well free of jaundice, regained weight 15 mos after operation
1941	Hunt (Case 2)	F	72	One-stage transduodenal excision and reimplantation common duct and duct of Wirsung T-tube choledochostomy	Living 33 mos after operation, no jaundice but with metastases
1941	Hunt (Case 3)	F	60	One stage Whipple operation, cholecystogastrostomy, posterior gastro enterostomy, resection of duodenum and part of head of the pancreas, division and ligation of common duct and duct of Wirsung	Recovered and in good health 1 yr after operation Pancreatic biliary fistula persisted until the 33rd postoperative day
1941	Hunt (Case 4)	F	43	First operation Cholecystectomy and T-tube choledochostomy Second stage Total duodenectomy and cautery excision of part of the head of the pancreas jejunopancreatostomy jejunocholedochostomy and posterior gastro enterostomy	Recovery T-tube removed from common duct on 8th postoperative day, no external biliary drainage after 11th postoperative day

|| Collected by Hunt in 1941

Postoperative and Subsequent Course—After three days, some pigment appeared in the bile as it drained from the choledochostomy tube, and the pigment became of gross normal concentration by the eighth day. The tube was removed on the eighteenth day and the patient was dismissed from the hospital on the twenty-ninth postoperative day with the wound healed and her general condition good. Ten months after the operation the patient had gained 35 pounds, and was feeling very well except for symptoms referable to the previously noted huge left hydronephrotic kidney. On July 1, 1935, a left nephrectomy was performed.

At about October 1, 1935, or 14 months after the original operation, the patient developed some discomfort in the chest and vomited occasionally. Six months later considerable weight had been lost and difficulty in swallowing was experienced. Subsequent esophagoscopic examination revealed a stricture at the level of the arch of the aorta. There never was recurrence of jaundice, but the patient's decline continued and death occurred, September 9, 1936, nearly 25 months after excision of the tumor of the ampulla.

Autopsy—Anatomic diagnosis (1) Extensive carcinoma of the retroperitoneal tissues and the mediastinum secondary to carcinoma of the ampulla of Vater. (2) Marked stenosis of the esophagus, trachea, and aortic arch from neoplastic involvement of the superior mediastinum.

Case 2—St Vincent's Hospital, No 3282-38. A woman, age 72 on May 13, 1938 stated that for 12 years she had had recurring attacks of upper abdominal pain, nausea

and vomiting There was some jaundice for a few days following an attack of pain 12 years ago Roentgenologic examination of the gallbladder was said to have visualized stones Following the last severe attack of upper abdominal pain three weeks before

FIG 1

FIG 2

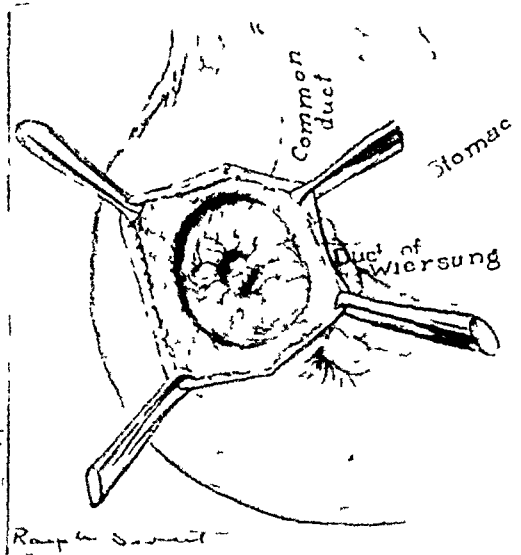
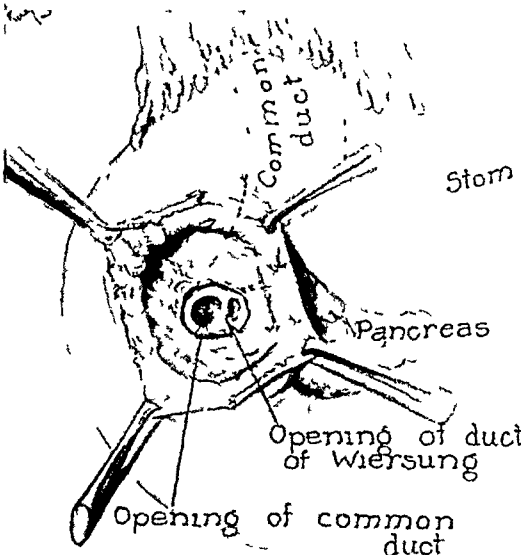
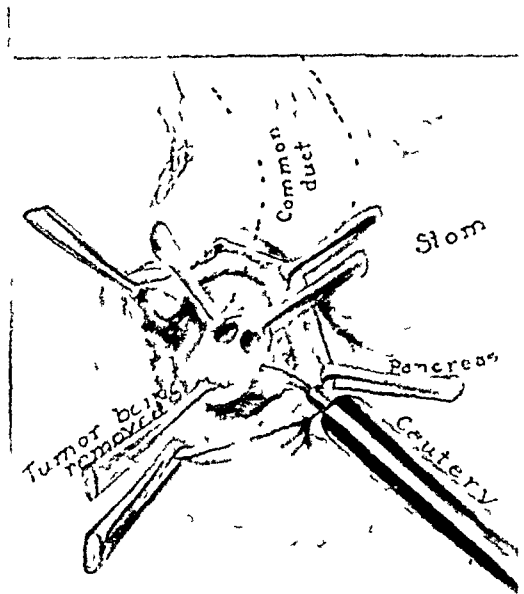


FIG 3

FIG 4

FIG 1—Tumor of the ampulla of Vater visualized upon opening the duodenum (Case 1)

FIG 2—Transduodenal cautery excision of tumor—method employed in Cases 1 and 2

FIG 3—Marked dilatation of the common and pancreatic ducts (Case 1)

FIG 4—Common and pancreatic ducts reimplanted into the posterior wall of the duodenum.

admission, the patient became moderately jaundiced and some jaundice persisted, with dark urine and clay-colored stools The patient had lost 20 pounds in weight

Upon examination, the patient was poorly nourished, weighed 84 pounds, and was moderately jaundiced Blood pressure 170/90 The liver edge was palpable at the level of the umbilicus and was tender The gallbladder was not palpable General physical examination was otherwise essentially negative

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Laboratory Data—Uranalysis Specific gravity 1.020, acid reaction, a trace of albumin, no sugar, and microscopic elements were absent with the exception of a few pus cells. The concentration of the hemoglobin was 13 Gm per 100 cc of blood (78 per cent), R B C 3,820,000, W B C 6,700, with a normal differential count, the bleeding time was

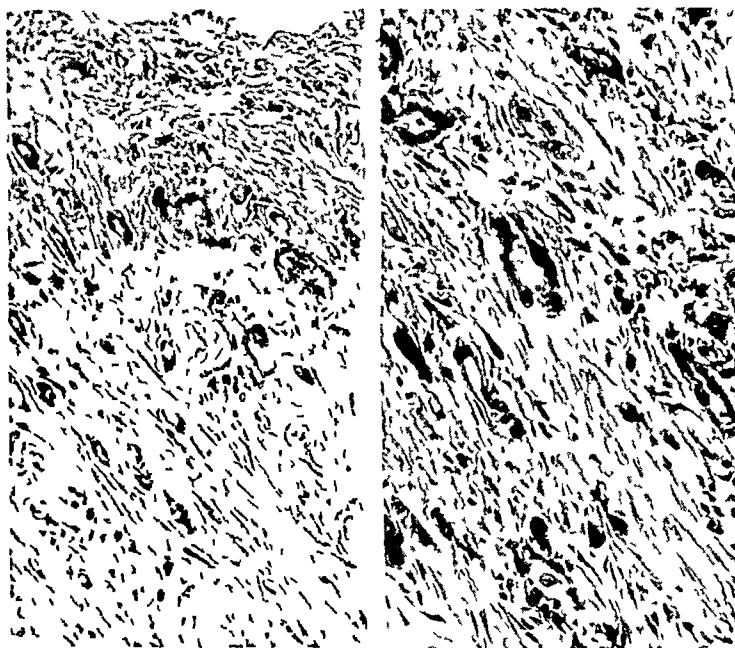


FIG 5 —Photomicrograph of Case 1 Adenocarcinoma, Grade III (left $\times 128$, right $\times 245$)

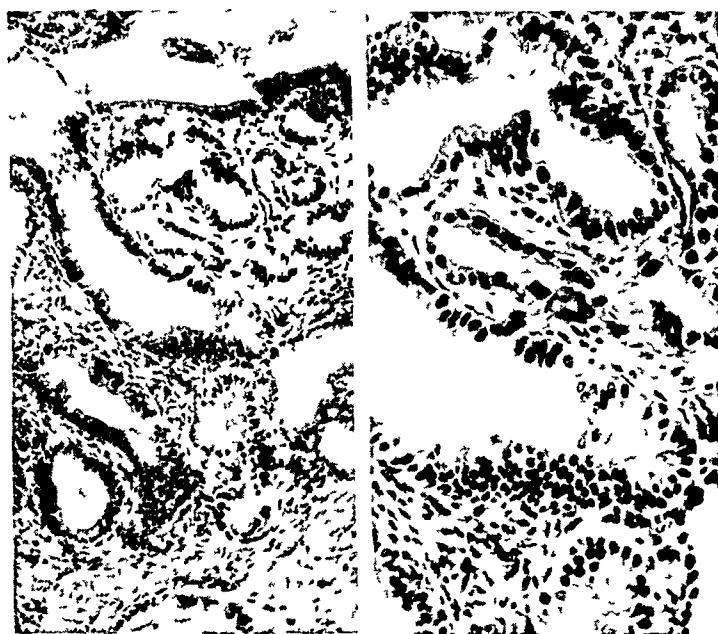


FIG 6 —Photomicrograph of Case 2 Adenocarcinoma, Grade III (left $\times 128$, right $\times 245$)

two minutes and the coagulation time was five and one-half minutes. A diagnosis of common duct obstruction, most probably stones, was made.

Operation—(Hunt) June 4, 1938. Transduodenal cautery excision of the ampulla of Vater, with reimplantation of the common duct and the duct of Wirsung into the posterior wall of the duodenum, and T-tube drainage of the common duct. The gall-

bladder was found to be greatly distended and the common duct was dilated to about 1.5 cm in diameter. Through aspiration of normal colored bile the gallbladder was collapsed and found to contain no stones. Exploratory choledochotomy was unproductive of stones in the common duct, but an olive-tipped probe met obstruction at the ampulla. A tumor, about 1 cm in diameter, in this area was palpable after the second and third portions of the duodenum had been mobilized. The anterior wall of the duodenum was incised and the tumor involving the ampulla proved to be mobile and not attached to the pancreas. A transduodenal cautery excision of the tumor was made as in Case 1, and, similarly, the severed dilated common duct and duct of Wirsung were reimplanted into the posterior wall of the duodenum. The incision in the duodenum was closed as was the fundus of the gallbladder at the site of its aspiration, and drainage of the common duct was instituted by a T-tube. *Pathologic Diagnosis* Adenocarcinoma of the ampulla of Vater. Grade III (Fig 6).

Postoperative and Subsequent Course—Twenty-four hours after operation the temperature was 102° F pulse 140, following which time improvement continued until the ninth day, when there was some gastric retention, which was controlled within 24 hours by gastric suction drainage. Convalescence continued satisfactorily. Lipiodol injection of the T-tube, on the eighteenth day, showed the material entering the duodenum, and the T-tube was removed. The patient was dismissed from the hospital on the forty-third postoperative day, with the wound healed and general condition good.

The patient remained entirely well until about October 1, 1939, approximately 15 months after the operation, when loss of appetite and weight occurred, with nausea, but no vomiting. Abdominal examination revealed a hard, nodular, tender mass in the upper right quadrant of the abdomen which suggested retroperitoneal metastases. There has been a gradual decline since that time, but on April 1, 1941, 34 months after operation the patient is still living, without recurrent jaundice, but with metastases.

Case 3—St Vincent's Hospital, No 2448-40. A woman age 60, stated, on March 13, 1940, that four months previously painless jaundice had developed and had become progressively more intense. A weight loss of 50 pounds had occurred from a normal weight of 185 pounds. There never had been any biliary colics or other symptoms referable to the biliary tract. The bowels had been constipated, and no gross blood had ever been observed in the stool. Marked edema of the lower extremities had developed during the preceding two months.

Upon examination, emaciation was marked and jaundice was intense. There were areas of excoriation and multiple pustules over the entire body and extremities. The weight was 136 pounds. Blood pressure 118/80. The positive findings on physical examination were the liver enlarged to the level of the umbilicus, a palpable, distended gallbladder, complete uterine prolapsus, and edema of the lower extremities to the knees (Grade 3).

Laboratory Data—Uranalysis. Specific gravity 1.019 acid reaction, albumin 3+, bile 4, no sugar, microscopic elements absent except for a few pus cells. The concentration of the hemoglobin was 14.4 Gm per 100 cc of blood (68 per cent), R B C 3,620,000, W B C 8,000, with a differential count within normal limits, the bleeding time was one minute and the coagulation time was four and one-half minutes. The prothrombin time was not taken until vitamin K and bile salts had been administered for four days, at which time it was 98 per cent of normal (patient 44 seconds, control 42 seconds). The urea content of the blood was 20 mg. No roentgenologic studies were carried out, as a diagnosis of carcinoma of the head of the pancreas or of the terminal common duct seemed justified. After 12 days' hospitalization and preoperative treatment operation was performed.

Operation—(Hunt) March 26, 1940. The Whipple procedure in one stage, resection of second and third portions of the duodenum and the head of the pancreas, ligation and division of the common duct, division and ligation of the duct of Wirsung, cholecystogastrostomy, posterior gastro-enterostomy and choledochostomy, and transfusion

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of 500 cc of citrated blood during the operation. The distended gallbladder was emptied of 150 cc of normal colored bile. There were no gallstones. The common duct was found to be dilated to fully 1.5 cm in diameter and admitted the index finger. A tumor, at least 2 cm in diameter, was palpated largely within the duodenum, but with some fixation and apparent involvement of the head of the pancreas. Through an incision in the anterior wall of the duodenum, the tumor was accurately visualized and its extent determined (Fig 7). Even though the tumor invaded the pancreas, it seemed to be an operable lesion, not through transduodenal excision, but through the utilization of Whipple's procedure. The duodenum was divided about 2 cm distal to the pylorus and the proximal duodenum was inverted. The distal duodenum was divided at approximately the juncture of the third and fourth portions and the distal duodenum was inverted.



FIG 7—Artist's illustration of the tumor in Case 3, visualized upon opening the duodenum. Insert is artist's illustration of sagittal section of tumor.

Approximately three inches of the duodenum containing the tumor were removed *en masse* with part of the head of the pancreas which was resected with the actual cautery during which procedure the common duct, 1.5 cm in diameter, and the duct of Wirsung, 8 mm in diameter, were divided, with the escape of fully an ounce of pancreatic secretion (Fig 8). The common duct and the duct of Wirsung were ligated with heavy silk. The severed surface of the pancreatic head was sutured with interrupted sutures of silk and the suture line covered with omentum. A T-tube was placed in the common duct, a cholecystogastrostomy was performed, and the operation completed by a posterior gastro-enterostomy (Fig 9). Two Penrose drains were inserted to the site of resection. *Pathologic Diagnosis*: Adenocarcinoma, Grade II, of the ampulla of Vater, with invasion of the pancreas (Fig 12).

Postoperative and Subsequent Course—Considerable shock was manifested, and on the day following the operation a transfusion of 600 cc of citrated blood was admin-

istered Progress was entirely satisfactory until the evening of the sixth day, when considerable bleeding occurred from the wound (It should be stated that suction drainage of the stomach had been instituted immediately after operation and vitamin K had been discontinued) A prothrombin time determination at the time of bleeding from the wound was 20 per cent of normal (patient 182 seconds, control 38 seconds) Immediate administration of vitamin K and bile salts controlled the hemorrhagic tendency On the day following the bleeding from the wound, profuse serous drainage oc-

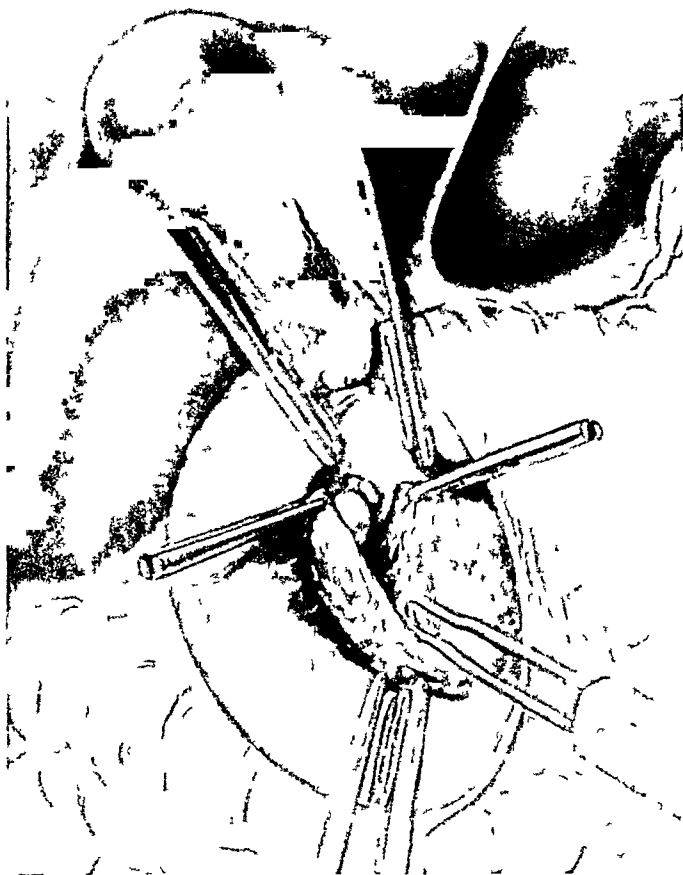


FIG 8—Artist's illustration of cautery resection of part of the head of the pancreas and second and third portions of the duodenum, *en bloc* in Case 3, marked dilatation of the common duct and duct of Wirsung

curred, which had the characteristics of pancreatic secretion This drainage continued copiously, and on the eighth postoperative day a catheter was inserted into the wound and through suction applied by the electric pump the wound was kept dry and the amount of secretion, which now contained bile, was measured Continuous suction was maintained for 19 days, or until the twenty-seventh postoperative day, and the amount of pancreatic secretion and bile from the wound was recorded (Table V) The sinus tract was then firmly packed with gauze, which allowed the wound to heal The patient was dismissed from the hospital, May 13, 1940, 48 days after operation, with the wound entirely dry The patient has been seen on a number of occasions, and has continued to make satisfactory progress She is entirely well, March 26, 1941, one year after operation, with no evidence of recurrence (Fig 13)

Case 4—St Vincent's Hospital, No 479-41 A woman, age 43, was admitted to St Vincent's Hospital, January 29, 1941 The patient's general health had been good until November, 1940 Thereafter, backache and digestive disturbances characterized by poor

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appetite, nausea and vomiting, and diarrhea without biliary colic comprised the chief complaint until about January 1, 1941, when jaundice developed, which became progressively more intense during the ensuing month. During this time 13 pounds loss of weight occurred.

Upon examination, the patient exhibited some emaciation and moderately deep, generalized icterus. Physical examination was essentially negative. Neither the liver nor gallbladder was palpable. Blood pressure 124/84, weight 103 pounds.



FIG 9—Artist's illustration of the operation completed in Case 3. Resection of part of the head of the pancreas and second and third portions of the duodenum *en bloc*, cholecystogastrostomy and posterior gastroenterostomy all accomplished in one stage.



FIG 10—Photograph of the resected duodenum in Case 3 showing the extent of the periampullary involvement of the duodenum.

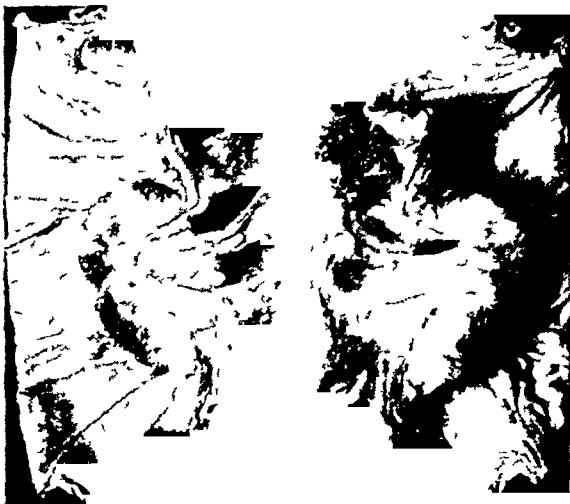


FIG 11—Photograph of sagittal section of the resected specimen in Case 3 showing marked dilatation of the common duct and duct of Wirsung, the projection of the tumor into the lumen of the duodenum, and invasion of the head of the pancreas by tumor.

Laboratory Data—Uranalysis gave negative results, with the exception of an occasional pus cell and red cell. The concentration of the hemoglobin was 10.5 Gr per 100 cc of blood (63 per cent), RBC 3,280,000, WBC 8,000, with approximately a normal differential count, blood cellular characteristics are here omitted. The prothrombin time was 93 per cent of normal, icteric index 30.2, the benzidine reaction for occult blood in the stool was positive. Gallbladder dye studies disclosed practically no dye in the gallbladder, but, instead, a calcified gallbladder was visualized. Films of the chest, kidneys, ureters, and bladder were negative. Roentgenologic examination of the stomach

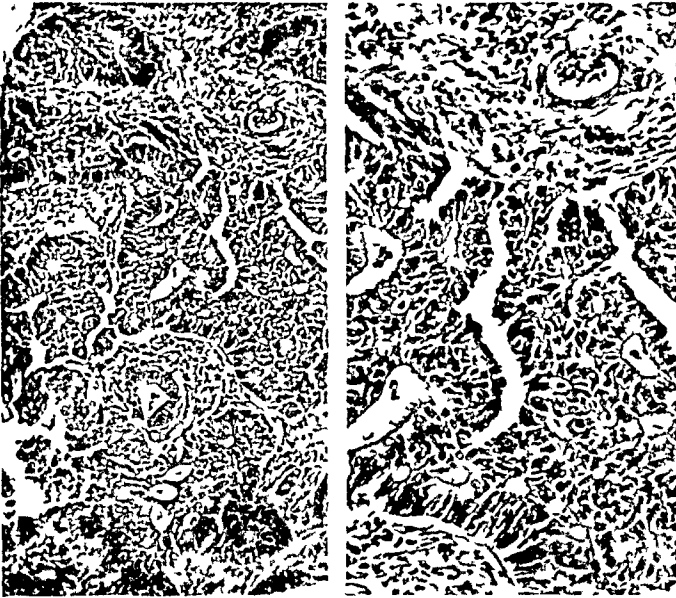


FIG 12—Photomicrograph of Case 3 Adenocarcinoma Grade II (left $\times 128$, right $\times 245$)

and duodenum was negative, except for hyperperistalsis and rapid clearance of the barium from the stomach. Fluoroscopic examination and films of the colon disclosed the absence of the right colon. *Preoperative Diagnosis*—Calculous disease of the gallbladder and common duct.

First Operation—(Hunt) February 1, 1941. Cholecystectomy for calculous disease of the gallbladder and T-tube choledochostomy. Upon opening the abdomen, a thick-walled gallbladder, adherent from a previous protective perforation, was found contracted down on a single large stone. The common duct was greatly dilated. However, exploratory choledochotomy was unproductive of stone in the common or hepatic ducts. An olive-tipped probe passed into duodenum with sufficient difficulty to suggest neoplastic obstruction of the terminal portion of the common duct. The duodenum was mobilized sufficiently for palpation of the second portion of the duodenum and head of the pancreas, in order to provide assurance (which subsequent events proved to be false) that neoplastic disease did not exist. The findings seemed to justify the assumption that pancreatitis existed and was responsible for the obstructive jaundice. T-tube drainage of the common duct was instituted. (Occult blood in the stool was disregarded.)

Postoperative Course—The T-tube was clamped off and the bile was diverted into the duodenum on the twelfth day, and no leakage of bile occurred for nearly a week, when profuse drainage of bile around the tube occurred. A cholangiogram, made on the nineteenth postoperative day, disclosed a complete block at the terminal portion of

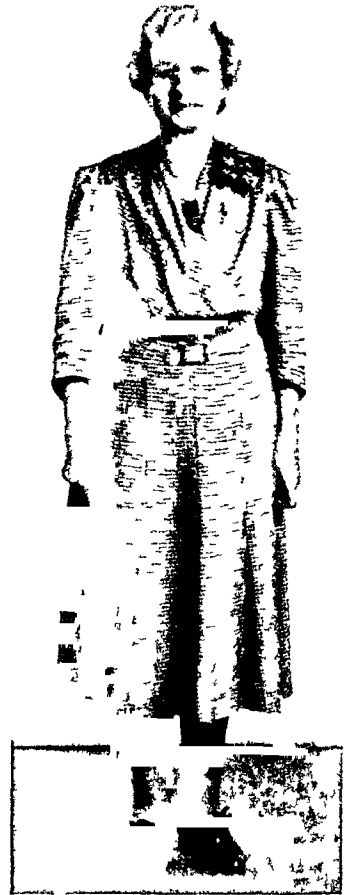


FIG 13—Photograph of the patient (Case 3) March 26, 1941 one year after operation

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the common duct. Cholangiographic studies were repeated on the thirty-second day, which again disclosed complete obstruction of the terminal common duct. Occult blood was again found in the stool, which, in spite of the previous findings at operation, justified the diagnosis of a tumor in the periampullary region of the duodenum.

Second Operation—(Hunt) March 5, 1941. Total duodenectomy and cautery excision of part of the head of the pancreas, jejunopancreatostomy, jejunocholedochostomy

FIG 14

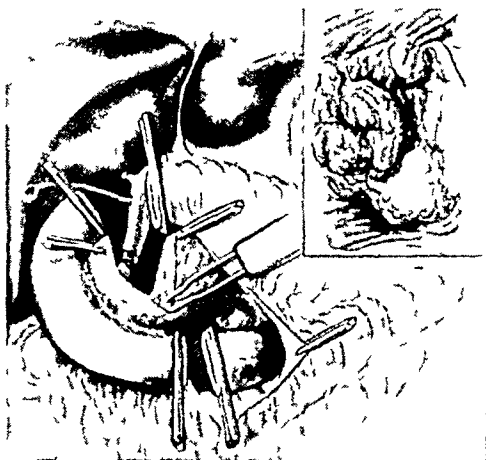


FIG 15

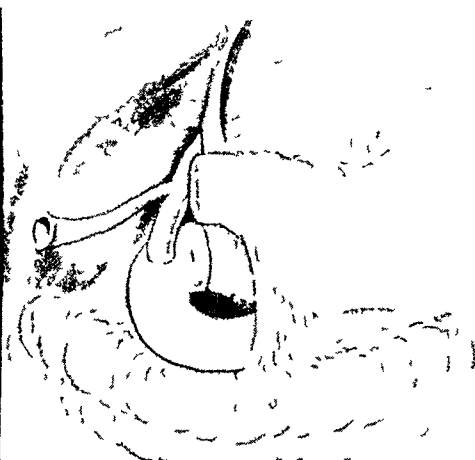


FIG 14—Artist's illustration of *en bloc* total duodenectomy and cautery resection of part of the head of the pancreas in Case 4 (cholecystectomy for calculous diseases of the gallbladder and T tube drainage of the common duct four weeks previously). Insert is artist's illustration of periampullary involvement of the duodenum.

FIG 15—Artist's illustration of operation in Case 4 completed by a long loop posterior gastroenterostomy, pancreaticojejunostomy and choledochojunostomy.

and posterior gastro-enterostomy, T-tube drainage of the common duct was maintained. Upon mobilization of the duodenum, an indurated, somewhat fixed mass in the posterior wall of the duodenum involving the head of the pancreas was encountered which, through an incision in the duodenum, proved to be a periampullary carcinoma. The incision in the duodenum was closed and an extensive resection was carried out. Because of the extensiveness of the induration, only through resection of the entire duodenum from the pylorus to well beyond the ligament or muscle of Treitz with cautery resection of part of the head of the pancreas, could the neoplastic involvement be removed (Fig 14). A long-loop posterior gastro-enterostomy facilitated drawing the proximal jejunum up through the opening in the transverse mesocolon to suture the open end of jejunum completely over the severed head of the pancreas in a manner to also include and receive the terminal portion of the common duct (Fig 15). A transfusion of about 600 cc of citiated blood was administered during the operation. *Pathologic Diagnosis*: Adenocarcinoma of the papilla of Vater, Grade III, with extensive involvement of the duodenum and extension to the head of the pancreas and adjacent lymph nodes (Fig 18).

Postoperative Course—At no time postoperatively did the temperature exceed 101° F. Drainage of bile around the loosely fitting T-tube was profuse for about five days, after which an electric suction pump facilitated measurement of the drainage which did not exceed 500 cc in 24 hours. The T-tube was removed from the common duct on the eighth day, and drainage of bile from the wound ceased on the eleventh postoperative day. There was no external loss of pancreatic secretion at any time. The patient was dismissed from the hospital in excellent condition on March 29, 1941, 24 days following the resection.

DISCUSSION—Usually, as carcinoma is encountered in this situation its exact site of origin is entirely indeterminate. Even though these lesions are frequently spoken of as ampullary carcinoma, there is much to support the idea that carcinoma arising within the true ampulla of Vater is extremely

rare Hanot termed this lesion *cancer du pylore pancratico-biliaire* to distinguish it from those periampullary lesions originating in other structures Lieber, Stewart, and Lund have recently verified the statements of Rolleston,

FIG 16



1 2 3 4 5 6 7 8 9 10 11 12 13 14 15

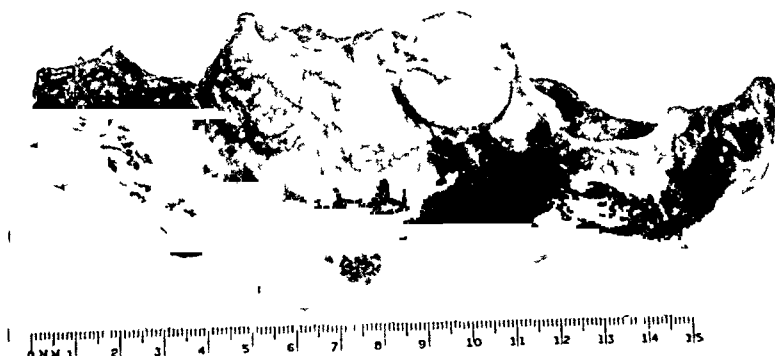


FIG 17

FIG 16—Photograph of the mucosal surface of the duodenum in Case 4 showing the extent of the tumor

FIG 17—Photograph of the exterior of the duodenum and resected head of the pancreas with several involved regional lymph nodes, marked dilatation of common duct. Duct of Wirsung entered the common duct proximal to the tumor and was not dilated (Case 4)

Springer, and others, in that, for the most part, these periampullary lesions are primary either in the terminal portion of the common duct, in the pancreatic duct, or in the intestinal mucous membrane overlying the papilla of Vater. As these lesions are encountered upon surgical exploration or at necropsy, all of these structures including the ampulla of Vater usually are involved in the neoplasm, and can be designated only under the broad term, neoplasm of the periampullary region of the duodenum. Practically all malignant lesions occurring in the periampullary region are carcinomata, most frequently adenocarcinoma or papillary carcinoma, although spindle cell sarcoma and melanoma have been reported.

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Early metastases are not frequent because, as Cooper has stated, the lesion, by virtue of its strategic position, produces obstructive symptoms early. However, that metastases to the retroperitoneal lymph nodes, liver, lungs, *etc*, may and do ultimately occur is attested by an incidence of such me-

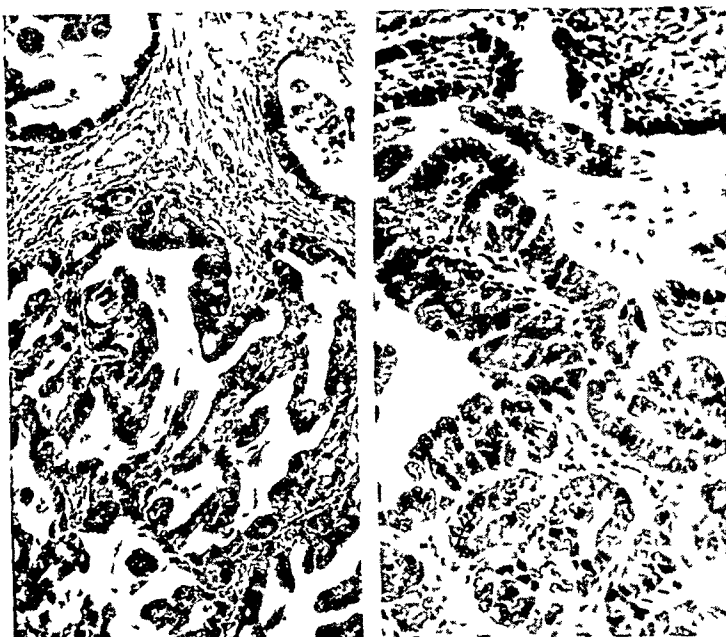


FIG 18—Photomicrograph of Case 4 Adenocarcinoma, Grade III
(left $\times 128$, right $\times 245$)

tastases in approximately 45 per cent of the cases reviewed by Lieber, Stewart, and Lund, which, for the most part, were the terminal findings at necropsy and not those of surgical exploration early in the course of the disease. Invasion of the pancreas was likewise a terminal finding at necropsy in 20 per cent of the cases.

Diagnosis—The clinical manifestations of periampullary carcinoma are practically always those of obstructive jaundice in which the distended gall-bladder, when palpable, in accordance with Courvoisier's law, leads to the diagnosis of neoplastic obstruction, usually carcinoma of the head of the pancreas. That error in the interpretation of diagnostic criteria may occur, is indicated by Ransom's study of 109 cases of carcinoma of the pancreas and bile ducts, verified by operation or at necropsy, in which the lesion in nine cases was periampullary. The relative frequency with which localized and entirely operable periampullary lesions are found at necropsy in individuals who have not been afforded the opportunity or who have been denied the privilege of surgical exploration through assumed clinical diagnostic accuracy and asserted futility, emphasizes the necessity for surgical exploration in all cases in which the clinical evidence indicates neoplastic obstruction of the terminal portion of the common duct.

Cooper, in 1937, and Lieber, Stewart, and Lund, in 1939, very thoroughly detailed the clinical manifestations of periampullary neoplastic disease. It is worthy of note that lesions in this situation occur in comparative youth. While the average age for 92 out of 124 cases (Table I), where the age was

recorded, was 50.9 years, the age was 35 years or less in eight cases, the youngest individual operated upon was age 17. In many instances pain was an important symptom, frequently of sufficient severity to warrant a diagnosis of calculous obstruction of the common duct, yet seldom was calculous disease of the common duct associated with periampullary neoplastic disease. The presence of occult blood in the stool may seldom be disregarded when obstructive jaundice exists. Denechau *et al* have suggested that biliary obstruction, intractable diarrhea and intestinal bleeding may give the clue to the diagnosis of ampullary carcinoma. In Cooper's study of 14 cases, occult blood was present in nine of 11 cases in which such investigation was made.

Roentgenologic studies have been of little diagnostic aid in early periampullary disease. Hoffman and Pack reported the roentgenologic findings in 16 cases of carcinoma of the duodenum, seven of which were periampullary lesions. Obstruction in the second portion of the duodenum was demonstrated in one of these, and in two cases there was six-hour gastric retention. Cooper reported the roentgenologic findings in ten cases of periampullary carcinoma. Obstruction at the level of the ampulla was noted in four cases, a filling defect in the duodenum in one case and some flattening of the posterior wall of the duodenum in another case. Positive roentgenologic findings in patients operated upon during recent years were exhibited in cases reported by Brunschwig and Childs, Roscher, and Ott. Cholangiographic studies revealing complete obstruction of the terminal portion of the common duct in conjunction with occult blood in the stool provided the basis for the clinical diagnosis of periampullary carcinoma in Case 4, herein reported.

Surgical Procedures—In 75 per cent of the 124 cases here collected, surgical extirpation of periampullary carcinoma was accomplished by transduodenal excision, and by retroduodenal excision, resection of the duodenum alone or with a part of the head of the pancreas in the remainder. In 21 cases, transduodenal excision alone was employed with apparently no attempt at restoration of biliary and pancreatic ductal continuity with the duodenum. In the 57 cases, however, in which the common and pancreatic ducts were divided in the course of excision of the tumor, these structures were reimplanted into the posterior wall of the duodenum. In approximately one-half of the cases in which these ductal structures were reimplanted, internal biliary drainage through some anastomotic procedure or external drainage of bile was provided. Internal or external drainage of bile was likewise provided in 15 cases in which the common duct and pancreatic ducts were not reimplanted. This latter procedure and resection of the duodenum with end-to-end anastomosis, and one or another of the various methods of disposing of bile and pancreatic secretion have proved the most hazardous methods of dealing with obstructing lesions in this situation (Table II).

Transduodenal excision, with one or another method of dealing with bile and pancreatic secretion, was actually employed in 85 per cent of the cases until about 1935. Advances which had been made in the surgical extirpation of adenomata of the islet cells of the pancreas and in resection of portions of the pancreas in hyperinsulinism paved the way for Whipple and his asso-

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TABLE II

SURGICAL PROCEDURES IN 124 RADICAL OPERATIONS FOR CARCINOMA OF THE AMPULLA OF VATER
(1898-1941)

Operation	No. of Cases	Deaths	Per Cent
Transduodenal excision	93	27	29.0
Transduodenal excision only	21	8	38.0
Transduodenal excision with reimplantation of common duct or common duct and pancreatic duct	30	5	16.6
Transduodenal excision with reimplantation of common duct or common duct and pancreatic duct with internal or external biliary drainage	27	7	25.9
Transduodenal excision without reimplantation of common duct or pancreatic duct with internal or external biliary drainage	15	7	46.6
Retroduodenal excision	5	2	40.0
Resection of duodenum with implantation of common duct or common duct and pancreatic duct and end-to-end anastomosis of duodenum	11	5	45.4
Resection of duodenum and head of pancreas	15	4	26.6
Total	124	38	30.6

ciates to devise and carry out the two-stage operation for periampullary carcinoma, wherein the duodenum and part of the head of the pancreas are resected *en bloc*. Since the presentation of this procedure by Whipple, Parsons, and Mullins, in 1935, approximately 50 per cent of the cases of periampullary carcinoma have been operated upon by their method.

Graham and others have demonstrated that a large part of the pancreas can be excised and that the main pancreatic ducts may be ligated, which has provided an approach to ampullary carcinoma invading the head of the pancreas inoperable to transduodenal methods. Biunschwig, in 1937, carried out, for the first time, this radical two-stage operation for carcinoma of the head of the pancreas. Preservation of external pancreatic secretion is desirable, but the problems of pancreato-intestinal anastomosis are great. Kerr suggested, in 1914, a method of capping the head of the divided pancreas with the distal end of the duodenum. However, the pancreatic capsule does not readily lend itself to such an anastomotic procedure. Tenani, in 1922, Nemenyi, in 1935, and Hunt in 1941, each accomplished such an anastomosis following resection of the duodenum and head of the pancreas for ampullary carcinoma.

The mortality rate of surgical extirpation of ampullary carcinoma in the 124 collected cases was 30.6 per cent. However, during the past 15 years the mortality rate has been materially reduced. In the 58 cases, collected by Cohen and Colp, the mortality rate was 41.3 per cent while in 66 cases operated upon since 1925 it was 21.2 per cent (Table III). A trend toward the two-stage operation has developed during the past 15 years, not only as pertains to radical resection of the duodenum and part of the head of the pancreas, but in transduodenal excision as well. Whereas there were eight

TABLE III

COMPARATIVE MORTALITY RATE IN 58 CASES (1898-1925), AND 66 CASES (1925-1941)

Operation	1898-1925			1925-1941		
	No of Cases	Deaths	Per Cent	No of Cases	Deaths	Per Cent
Transduodenal excision	46	20	43.4	47	7	14.9
Transduodenal excision only	16	8	50.0	5	0	0
Transduodenal excision with reimplantation of common duct or common duct and pancreatic duct	15	3	20.0	15	2	13.3
Transduodenal excision with reimplantation of common duct or common duct and pancreatic duct with internal or external biliary drainage	8	4	50.0	10	3	15.8
Transduodenal excision without reimplantation of common duct or pancreatic duct with internal or external biliary drainage	7	5	71.0	8	2	25.0
Retroduodenal excision	4	2	50.0	1	0	0
Resection of duodenum, with implantation of common duct or common duct and pancreatic duct and end to end anastomosis of duodenum	8	2	25.0	3	3	100.0
Resection of duodenum and head of pancreas	0	—	—	15	4	26.6
Total	58	24	41.3	66	14	21.2

two-stage operations in the first 58 cases, collected by Cohen and Colp, there were 20 two-stage operations in 66 cases, collected since 1925, with a mortality rate of 25 per cent as compared to 19.5 per cent in 46 one-stage operations.

In the past, operative and postoperative bleeding has been the chief hazard of the surgical procedures for extirpation of ampullary carcinoma. Hemorrhage accounted for 31 per cent of the deaths, when the cause of death was stated (Table IV). However, it is more than probable that the cause of

TABLE IV

CAUSE OF DEATH IN 38 CASES (1898-1941)

Cause	No of Cases	Per Cent
Hemorrhage	12	31.5
Peritonitis	5	13.1
Duodenal fistula	3	7.8
Shock	2	5.2
Pneumonia	2	5.2
Not stated	14	36.8

death was hemorrhage in fully 50 per cent of the cases, had the cause of death been stated in each instance. Peritonitis, duodenal and pancreatic fistula, shock and pneumonia likewise have been rather prominent and important causes of death. Among the postoperative complications, duodenal and pancreatic fistulae materially prolong convalescence and provide many problems in their management.

Pancreatic Fistula—The amount of secretion which may be lost through the wound once a pancreatic fistula develops is at times surprisingly large, particularly when the secretion consists of all the pancreatic secretion and bile. Snyder and Lium, who intubated the duct of Wirsung following transduodenal excision of a carcinoma of the ampulla, collected the pancreatic secretion for 12 days. There was great variation in the amount of pancreatic secretion each 24 hours, as influenced by many factors. However, during the last four days in which drainage was maintained, the average daily output

TABLE V
DAILY 24-HOUR OUTPUT OF PANCREATIC SECRETION AND BILE
(CASE 4) BY SUCTION DRAINAGE

1940		Amount Cc
April 4	From 9 30 A M	1 350
April 5		1 030
April 6		1 800
April 7		1 975
April 8		1 680
April 9		1 550
April 10		1,680
April 11		1,575
April 12		1,250
April 13		750
April 14		1,500
April 15		1,470
April 16		1,600
April 17		1,180
April 18		1,200
April 19		1 130
April 20		920
April 21		1,200
April 22		940
April 23	7 00 A M to 10 50 A M	175
April 27	From 10 50 A M	1 100
April 28	7 00 A M to 11 45 A M	350

of pancreatic secretion was 1,167 cc, with a maximum of 1,384 cc. Bile-tinged secretion amounting to as much as 1,500 cc in 24 hours in Ransom's case practically ceased by the eighteenth postoperative day. In my own Case 3, the measured daily output of secretion consisting of bile and pancreatic secretion averaged 1,356 cc for 19 days, with a maximum 24-hour output of 1,975 cc (Table V). A tendency exists for a pancreatic fistula to cease draining spontaneously if and when communication with the intestinal tract occurs. Such spontaneous closure apparently occurred in the cases of Ransom, Hunt, and Hollenberg, even though eight to nine months elapsed in the latter case. A pancreatic fistula persisted in Orr's case at seven months, and after three months in Orator's case. In the latter instance, external diversion of secretion from the fistula to a jejunostomy was accomplished.

Results of Operation—In general, the results of surgical extirpation of ampullary carcinoma have not been good (Table VI). The follow-up is entirely inadequate, and the ultimate result in those surviving the operation is not known, except as it was, for the most part, obtained from the original case report. The information available to me disclosed that 41 per cent of

TABLE VI

RESULTS IN 86 CASES WHICH SURVIVED RADICAL REMOVAL OF CARCINOMA
OF THE AMPULLA OF VATER AND PERIAMPULLARY PORTION OF THE DUODENUM

Subsequent course not recorded	15
Reported living and well	36
1-6 months	8
6-12 months	11
12-18 months	5
2 years	2
3 years	4
4 years*	3
5 years	1
8 years	1
9 years	1
Living with pancreatic fistula	2
3 months and 7 months	
Living with metastases	2
23 months and 3 years	
Death from recurrence or metastases	26
Within 6 months	10
6-12 months	6
12-18 months	1
18-24 months	3
24-30 months	4
30-36 months	1
56 months	1
Death from other causes without evidence of recurrence or metastases	5
8-12 months	3
2 years	1
3 years	1

* One of these (Koerte's Case 2) was reported by Muller and Rodemaker also by Whipple, Parsons and Mullins to have survived 22 years

the patients surviving the operation were living and well up to nine years. One of these, Koerte's Case 2 (Table I), operated upon in 1905, was reported by Muller and Rodemaker, and also by Whipple, Parsons, and Mullins to have survived for 22 years. Two other cases (Van Ardenne and Van Remynse) which were not available to me, were reported by Muller and Rodemaker living five and six years, respectively. It would appear that perhaps 12 persons, or approximately 14 per cent, of those who survived the operation were living and well for periods varying from three to 22 years. That one may live for some time, even with recurrence and metastases, is proved by the case reported by Muller and Rodemaker, in which the patient survived four years and eight months after operation. Death from recurrence or metastases occurred in 30 per cent of the cases within one year or thereabouts, but several patients lived for from two and one-half to three years.

That radical surgical procedures are warranted early in periampullary carcinoma, is emphasized by the statistical review of Lieber, Stewart, and Lund. Ninety-seven of 100 patients who were not operated upon lived from two weeks to 28 months, an average of 6.6 months. Sixty-one, or two-thirds of these, died within six months, while 90 per cent lived less than one year, and interestingly enough, four lived for from 22 to 28 months. Palliative operation was performed for the relief of jaundice, with a mortality rate of 76.4 per cent within the first 19 days, nine survived from one to 60 months,

an average of 19 months, and three were living at the end of four, four and one-half, and 42 months, respectively. Certainly, the mortality rate of radical operation throughout the entire period since Halsted's first radical operation, has been materially less than that for palliative operations. Judd and Hoeimer have stated that patients who survive resection or excision live longer than those in whom simple palliative operations are performed.

Even though part of the head of the pancreas was included in the resection of the duodenum for periampullary carcinoma by Kausch, in 1909, Hirschel, in 1913, Tenani, in 1922 and Denks, in 1929, the radical operation of Whipple, Parsons, and Mullins provides a method for resection wide of the lesion, through which hope may be engendered for improvement in the ultimate results of surgical extirpation of periampullary neoplastic disease.

SUMMARY

Four cases are reported in which carcinoma of the periampullary portion of the duodenum was successfully removed. Transduodenal resection of the ampulla of Vater and terminal portion of the common and pancreatic ducts, with reimplantation of these ducts into the posterior wall of the duodenum comprised the surgical procedure in two cases, the various procedures facilitating resection of the duodenum and head of the pancreas by the method of Whipple, Parsons, and Mullins in two stages was successfully carried out in one-stage in one case, in the fourth case, cholecystectomy for calculous disease of the gallbladder and T-tube drainage of the common duct preceded the second-stage operation of total duodenectomy, resection of the head of the pancreas, pancreaticojejunostomy, choledochojejunostomy and posterior gastro-enterostomy.

A collective review of 124 cases of radical operation for ampullary carcinoma is presented, which provides the basis for an analysis of the various surgical procedures, their mortality rate, and the results, in general, of radical extirpation of neoplastic disease in this situation.

Abstracts of 32 cases, not previously collected, are appended.

ABSTRACTS OF 32 CASE REPORTS OF RADICAL OPERATION FOR CARCINOMA OF THE AMPULLA OF VATER, COLLECTED SINCE 1935*

*The first 11 of these were operated upon previous to 1935, but were not included in the collective reviews of Cohen and Colp, in 1927, Hunt and Budd in 1935, or by Whipple, Parsons, and Mullins in 1935.

BOHM (reported by Keil). The patient, a man, age 52, six weeks previous to admission, developed jaundice not accompanied by pain, loss of appetite, weight or strength. A diagnosis was made of tumor of the head of the pancreas or the ampulla of Vater. At operation, May, 1910, transduodenal excision of a hazelnut sized tumor of the ampulla was made and the common duct and the duct of Wirsung were reimplanted into the posterior wall of the duodenum. The pathologic report was adenocarcinoma.

Subsequent Course. Two years after operation the jaundice recurred and a posterior gastro-enterostomy was performed for local recurrence. The patient lived nearly one year thereafter.

SCHUSSLER (two cases). Case 1.—The patient, a man, age 43, had had painless jaundice for three months. At operation a tumor at the ampulla of Vater was found. A resection of the duodenum was performed and the common duct and duct of Wirsung were reimplanted into the duodenum. The patient died of hemorrhage on the ninth day. The pathologic report was carcinoma of the ampulla of Vater.

Case 2—A woman, age 34, had had severe biliary colic and jaundice of five weeks' duration. At operation, July 12, 1919, a transduodenal excision of the tumor of the ampulla was made and the common duct was reimplanted into the duodenum. A posterior gastroenterostomy was added. The patient was reported to be in good health at the end of four months. The pathologic report was carcinoma of the ampulla of Vater.

BLAD. The patient, a woman, age 62, had for eight months gradually progressive jaundice and hemorrhage from the nose and from the intestinal tract. At operation, February 24, 1920, a tumor about the size of an olive was palpated at the terminal portion of the common duct. A transduodenal excision of this tumor was made with reimplantation of the common duct into the duodenum, 16 months after operation the patient was in good health. The pathologic report was adenocarcinoma of the ampulla of Vater.

BRENNER (reported by Eppinger and Walzel). The patient was a man, age 58, who had had occasional gallbladder colics for nine years. Previous to admission, there had been upper right quadrant pain followed by jaundice. At operation in November, 1924, a tumor was palpated in the second portion of the duodenum. The duodenum was incised and the tumor of the posterior wall of the duodenum was excised. The case is reported by Eppinger and Walzel as one of neoplastic obstruction of the terminal portion of the common duct.

EISENBERG (reported by Eppinger and Walzel) (two cases). Eppinger and Walzel report two cases of carcinoma of the ampulla of Vater which were removed by transduodenal excision. No statement is made of the disposition of the common duct or the duct of Wirsung. Recovery occurred in one of these patients and the other patient died on the third day of hemorrhage.

IAGOS, UGON, AND DOMINGULZ. The patient, a man, age 41, had painless progressive jaundice of three months' duration. A diagnosis was made of probable neoplasm of the head of the pancreas. At operation in April, 1926, a transduodenal excision of a small tumor at the ampulla of Vater, a little less than 1 cm. in diameter, was accomplished. The common duct was reimplanted into the posterior wall of the duodenum. Death occurred 16 hours later from hemorrhage. The pathologic report was carcinoma of the ampulla of Vater.

DE BEULE (three cases). The author operated upon three cases of carcinoma of the ampulla of Vater. In each of two patients the tumor, the size of a hazelnut, was removed by transduodenal excision with reimplantation of the common duct into the posterior wall of the duodenum. In one of these patients, massive metastases to the liver occurred within a few months after operation. The other patient survived for three years and died of influenza. The tumor in the third patient, the size of a pigeon's egg, was ulcerating and was removed by resection of the duodenum with end-to-end anastomosis following which a cholecystogastrostomy was performed. This patient died following the operation.

SNYDER AND LIUM. The patient, a man, age 48, was admitted to the hospital March 31, 1934, with a history of jaundice of 12 weeks' duration and a loss of weight of 35 pounds. At operation, a firm tumor about 1.5 cm. in diameter, at the ampulla of Vater was palpated. Cholecystoduodenostomy was performed and the common duct was drained. Five weeks later, a transduodenal excision of the tumor of the ampulla of Vater was performed. A catheter was inserted into the dilated duct of Wirsung after the duct had been reimplanted into the posterior wall of the duodenum, and the catheter was brought out through the duodenum and anterior abdominal wall. Catheter drainage of the duct of Wirsung was maintained for 11 days. During the last four days of this period the average daily output of pancreatic secretion amounted to 1167 cc. A subsequent local recurrence necessitated another surgical procedure, with recovery. Pathologic studies proved the tumor to be carcinoma, probably originating in the common duct.

KAFKA. A man, age 52, had progressive, painless jaundice for about four months. At operation, October 9, 1935, transduodenal excision of a bean-sized tumor at the ampulla was accomplished and the common duct and the duct of Wirsung were reimplanted into the posterior wall of the duodenum. Twenty months after the operation the patient was entirely well, but two years after the operation death occurred from unknown cause. The pathologic report was carcinoma.

NEMENYI. The patient, a man, age 42, had had progressive, painless jaundice for three months with a loss of weight of 40 pounds. At operation, December 12, 1935, a tumor was palpated at the ampulla of Vater. The duodenum containing the tumor and a small section of the pancreas were resected. The pancreatic duct was not seen, but the common duct traversed the pancreas remaining. The distal, open end of the duodenum was sutured over the head of the pancreas. A loop of jejunum was anastomosed to the proximal duodenum and an enteranastomosis was made between the two limbs of the jejunum. Sixteen months after the operation the patient was entirely well, having regained nearly all his weight. The pathologic report was adenocarcinoma of the ampulla of Vater.

BUMM (reported by Geisthovel). A man, age 54, had had digestive disturbance for about two years, without biliary colic and had been jaundiced for about 18 months. There had been occasional chills and fever and the patient had lost 30 pounds in weight. At operation, in February, 1936, a cherry stone-sized tumor at the ampulla of Vater was exposed through an incision in the duodenum. A transduodenal excision of the tumor was accomplished and the common duct and the duct of Wirsung were reimplanted into the posterior wall of the duodenum. A cholecystoduodenostomy was made at the site where the duodenum had been opened. Six months after operation the patient had gained 22 pounds, and was well. The pathologic report was carcinoma of the ampulla of Vater.

PERIAMPULLARY CARCINOMA

ORATOR A woman, age 48, had had epigastric discomfort for two months, loss of appetite, and only slight jaundice. Roentgenologic examination disclosed an obstructing lesion of the duodenum. At operation, January 25, 1936, a hen's egg sized tumor of the duodenum attached to the head of the pancreas was found. A posterior gastroenterostomy and cholecystogastrostomy comprised the first stage operation. On February 6, 1936, 12 days later, the second stage resection of the duodenum and head of the pancreas, was performed, after the method of Whipple, Parsons and Mullins. A pancreatic fistula developed shortly after operation and the daily loss of pancreatic secretion varied between 300 and 500 cc, which by the end of about four weeks decreased to 200 cc. With a pancreatic fistula persisting a high jejunostomy was performed, so that the pancreatic secretion from the fistula could be injected into the jejunum. The subsequent course is not reported. The pathologic report was annular adenocarcinoma of the duodenum with invasion of the pancreas.

HYDE AND YOUNG A woman, age 76, was admitted to Faulkner Hospital, October 26, 1936, on account of jaundice for two weeks. Blood in stool by guaiac test ++ on one of two occasions. *Preoperative Diagnosis* Carcinoma of the pancreas. At operation, November 17, 1936, transduodenal excision of a tumor of the ampulla of Vater, 1.5 by 1 by 0.6 cm in diameter, with reimplantation of the common duct and the duct of Wirsung into the posterior wall of the duodenum was accomplished. The common duct was drained externally. Annual follow up studies have revealed an apparent cure after three years. The pathologic report was adenocarcinoma of the ampulla of Vater.

HOLLENBERG (personal communication from Whipple) The patient, a woman, age 45, was mildly jaundiced and had lost 30 pounds in weight. There was blood in the stool. In March, 1936, the first stage of the Whipple operation was performed, and one month later a resection of the duodenum and part of the head of the pancreas was accomplished for a carcinoma of the ampulla of Vater, about 3 cm in diameter. A nonirritating pancreatic fistula developed which persisted for eight to nine months. Following lipiodol injection of the sinus, which disclosed communication with the small intestine, the drainage ceased spontaneously. Thereafter excellent health was experienced for a year and a half. Clinical manifestations of local recurrence developed without jaundice and death occurred in February, 1939, slightly less than three years after the resection.

HOFFMAN AND PACK A man, age 58, had recurrent jaundice, chills and fever. A diagnosis was made of an impacted stone in the common duct. At operation, by Doctor Pickhardt, the common duct was found to be obstructed at the ampulla, but no stone was found, and the common duct was drained by a T tube. At the end of four weeks a copious hemorrhage occurred from the gastrointestinal tract and from the wound. Following transfusion, a tumor involving the ampulla of Vater which was excised. Death occurred six hours later. The pathologic report was adenocarcinoma.

MALLET GUY A woman, age 56, had had repeated biliary colic, chills, fever and jaundice, had been operated upon several times and stones had been recovered from the common duct. At operation, April 8, 1938, a transduodenal excision of a small tumor obstructing the ampulla of Vater was performed, and the common duct was drained externally. Recovery occurred. The pathologic report was epithelioma(?)

MCCABE The patient, a man, age 67, had had painless jaundice for three months, during which time the weight loss was 30 pounds. Epigastric pain, vomiting and diarrhea were manifested during the three weeks preceding admission. At operation, July 16, 1937, a tumor the size of a hen's egg, mobile and soft in consistency, was palpated in the second portion of the duodenum and transduodenal excision of the tumor was performed. The common duct and the duct of Wirsung were reimplanted into the posterior wall of the duodenum. The common duct was drained by a T tube. Bleeding from the wound, stomach, bowel and kidneys occurred on the fifth postoperative day and continued for a week, finally subsiding following daily transfusion. The convalescence thenceforth was entirely satisfactory. The pathologic report was adenocarcinoma.

BRUNSCHWIG AND CHILDS The patient, a woman, age 41, was admitted, October 22, 1937, chiefly because of increasing fatigue, an increase in the quantity of stool and irregular periods of frequent stools. The stools had been foul and varied in color from clay colored to dark brown. There was no history of jaundice. Upon examination, a vague, deep mass the size of an egg was palpable to the right and slightly above the umbilicus. The stools contained occult blood. Roentgenographic examination disclosed a tumor mass, approximately 8 by 5 cm, within the distended second portion of the duodenum. The preoperative clinical diagnosis was a neoplasm of the pancreas or duodenum with partial obstruction of the pancreatic ducts. At operation, November 26, 1937, a one stage transduodenal excision of the tumor was performed with reimplantation of the common duct and the duct of Wirsung into the posterior wall of the duodenum. At the end of 15 months the weight had been regained and there was much improvement in the patient's general condition. The pathologic report was carcinoma (possibly carcoid) of the second portion of the duodenum with involvement of the ampulla of Vater.

ROSCHER The patient, a man, age 55, had loss of appetite and weight and progressive obstructive jaundice for four to five months. Roentgenologic examination of the stomach and duodenum disclosed what was interpreted as an ulcerating tumor in the region of the papilla of Vater. At operation, in March, 1936, a cholecystogastrostomy was performed. Two months later the second stage resection of the duodenum and part of the head of the pancreas, division and ligation of the common duct, implantation of the duct of Wirsung into the jejunum and posterior gastroenterostomy

were performed. Death occurred five months after operation of bronchopneumonia. The pathologic report was carcinoma of the papilla of Vater.

DIVIS (reported by Křík, 1937) The patient was a woman age 65 who had in obstructive jaundice. April 30 1937, stones were removed from the gallbladder and one stage transduodenal excision of tumor, with reimplantation of the common duct and duct of Wirsung into duodenum and cholecystoduodenostomy were accomplished. Death occurred one year after the operation from a cardiac lesion.

TROUT The patient, a man, between 55 and 60 years of age was operated upon for a carcinoma of the ampulla of Vater, with invasion of the head of the pancreas. The operation consisted of cholecystojejunostomy, posterior gastroenterostomy, division and ligation of the common duct just below the cystic duct, resection of the duodenum and head of the pancreas *en bloc* in one stage. Death occurred within a few hours after the operation.

RIVER McNEALY AND RAGINA (three case reports) Case 1—(McNealy) A woman, age 63 was admitted to the Cook County Hospital December 12 1937 with the complaint of dull boring epigastric pain and progressive jaundice of four weeks' duration. The stools contained occult blood on several occasions. A diagnosis of obstructive jaundice probably due to a malignant lesion was made. At operation, January 8 1938 transduodenal resection of a tumor of the ampulla of Vater was made and the common duct and duct of Wirsung were reimplanted into the posterior wall of the duodenum. Approximately 16 months later jaundice, chills and fever recurred. At operation August 23 1939 cicatricial stenosis at the site of the reimplantation of the common duct into the posterior wall of the duodenum was found. A cholecystogastrostomy was performed. The patient was well two years and two months following excision of the tumor. The pathologic report was adenocarcinoma of the ampulla of Vater with invasion of the common duct and the pancreatic duct.

Case 2—(River) The patient, a man age 55, was admitted to the Cook County Hospital July 4 1939, because of jaundice of eight months duration, loss of 58 pounds in weight and pain in the upper right quadrant of the abdomen. At operation July 20 1939 the common duct and the gallbladder were drained. Jaundice recurred at the end of three weeks immediately following closure of the biliary fistula. The persistence of blood in the stool suggested the diagnosis of carcinoma of the ampulla of Vater. Operation August 15 1939 consisted of transduodenal excision of the ampullary tumor with reimplantation of the common duct into the posterior wall of the duodenum. Eight months later jaundice, chills and fever suggested cicatricial stenosis of the common duct. A cholecystojejunostomy after the method of Whipple was followed by recovery. The pathologic report was adenocarcinoma of the terminal portion of the common duct.

Case 3—(River) The patient a man age 55 years was admitted to the Cook County Hospital, September 6 1939 on account of jaundice of four weeks duration pain in the upper right quadrant of the abdomen and weight loss of ten pounds. At operation September 29 1939 transduodenal excision of a tumor 1.3 cm in diameter at the ampulla of Vater was made and the common duct and the duct of Wirsung were reimplanted into the posterior wall of the duodenum. External drainage of the biliary tract was provided by cholecystostomy. The patient was entirely well nine months later. The pathologic report was papillary adenocarcinoma of the pancreatic duct.

MADDOCK A man age 36 was admitted to the University of Michigan Hospital January 13, 1940, on account of jaundice and intermittent diarrhea of three months duration. The patient had had severe stabbing pain in the upper right quadrant of the abdomen. At operation January 22 1940, an incision in the duodenum exposed a tumor of the ampulla of Vater. A resection of the second portion of the duodenum including the tumor was accomplished with end to end anastomosis, restoration of the duodenum. The common duct was implanted into the first portion of the duodenum and the gallbladder was removed. Death occurred on the fourteenth day from peritonitis. The pathologic report was adenocarcinoma of the ampulla of Vater.

ORR The patient, a man age 47 was admitted to the University of Kansas Hospital April 24 1940 on account of painless, progressive jaundice and weight loss of 30 pounds during the preceding four months. Operation—First stage. Upon surgical exploration April 30, 1940 a firm mass 1 cm in diameter was palpated at the ampulla. An anastomosis between the common duct (gallbladder absent) and the stomach was made and a posterior gastroenterostomy completed the first stage operation. Second stage operation—May 15 1940. The terminal common duct was ligated and divided the duodenum from the pylorus to well below its second portion and a wedge shaped section of the head of the pancreas were resected. The pylorus and distal duodenum were closed and the defect in the pancreas was closed with interrupted sutures of silk. Following the operation there was profuse drainage of clear fluid from the wound. The patient was readmitted to the hospital several times subsequently on account of persistence of the pancreatic fistula. Seven months after operation the patient had regained the 25 pound weight loss. Moderate drainage from the pancreatic fistula persisted. The pathologic report was adenocarcinoma of the ampulla of Vater.

RANSOM J K a man was admitted to the University of Michigan Hospital, December 14 1940 on account of painless progressive jaundice of one month's duration and a weight loss of 12 pounds. *Clinical Diagnosis* Obstructive jaundice probably due to carcinoma of the head of the pancreas. Operation—December 24 1940. A movable olive sized tumor was found at the ampulla of Vater. The first stage of the Brunshwig operation was carried out which consisted of a posterior gastroenterostomy, cholecystojejunostomy and enteroanastomosis between the two limbs of jejunum. At the second operation January 21 1941 the resection included the first and second portions of

the duodenum and the head of the pancreas. The pyloric end of the stomach and distal duodenum were closed, the pancreatic duct and the common duct were ligated, and the end of the pancreas was closed with mattress sutures. On the fourth day after operation a moderate amount of clear fluid drained from the wound which two days later became biletinged. At one time the fistulous tract drained as much as 1500 cc in 24 hours. By the eighteenth postoperative day drainage from the wound had practically ceased. Twenty five days after the resection the patient was still in the hospital, but was progressing satisfactorily.

WHIPPLE. The patient a man, age 58, was operated upon in October, 1939 for carcinoma of the ampulla of Vater, in whom the radical two stage operation was performed with excision of the duodenum and part of the head of the pancreas. This patient is well has regained his weight, is free from jaundice, and has no digestive disturbance, 15 months after operation.

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DISCUSSION—DR MORRIS K SMITH (New York, N Y) I have recently had an experience with a case which corresponded in many ways to Doctor Hunt's last patient. As the matter of diagnosis is almost as difficult as the treatment, it seems worth while to emphasize the point Doctor Hunt made of the significance of blood in the stool.

In my patient I performed a cholecystectomy and drainage of the common duct, but failed to feel a tumor in the duodenum. After two weeks, the stools continuing clay-colored and bile drainage as profusely as ever, a cholangiogram was made which showed a smooth contour of the dilated duct with complete block at the duodenal end. The patient, who had been carefully studied in hospital prior to operation, had shown one unexplained and persistent finding—*occult blood in the stool*. This combination of bleeding and obstruction at the terminus of the common duct, as in Doctor Hunt's case, pointed the way to the diagnosis.

In my patient, we made one further test, duodenal intubation, and obtained contents which were grossly bloody. At the second operation a periampullary carcinoma of the duodenum, resembling grossly the ordinary carcinoma of the large bowel, was found.

DR THOMAS E JONES (Cleveland) Many of these cases are deeply jaundiced when they come in for surgery. At operation, we do not know about the patency of the cystic duct. If cholecystogastrostomy is performed, very often there may be a kinking near the duct, and many of these cases will die before they reach the second stage, because we do not get good biliary drainage.

To obviate this difficulty, in the successful case which I had I put a T-tube in the common duct. This gives good drainage immediately, and at the second-stage the patient is in very much better condition. In the first-stage I used a T-tube drainage of the common duct and established a gastro-enterostomy. In the second-stage we removed the head of the pancreas and anastomosed the common duct to the jejunum. The case developed a pancreatic fistula, but he was able to leave the hospital in 36 days. This was about four months ago, so the end-result is not known.

DR DALLAS B PHEMISTER (Chicago) There have been three cases operated upon in our clinic—16 months, two and a third years, and three years ago—by the technic described by Doctor Hunt for his first case, which have remained well. In two cases an additional cholecystogastrostomy was performed for fear there might be subsequent stenosis of the common duct. I do not know that it made any difference.

The question of roentgenologic diagnosis was referred to. In one of these patients the roentgenologist did not locate the lesion, but we did not send the patient in with the presumptive diagnosis of carcinoma of the ampulla. In one case, the patient entered with a cholecystotomy sinus, and we injected lipiodol through the fistula. The gallbladder and bile ducts filled, and obstruction was shown at the outlet of the common duct. The patient was reexamined, a barium meal being given first, which showed a defect in the region of the ampulla. Then the gallbladder and bile duct were injected. Both methods of examination confirmed the diagnosis of carcinoma of the ampulla. I think that if such patients are sent to the roentgenologist with the tentative diagnosis of ampullary pathology they will more frequently recognize the lesion.

DR THOMAS G ORR (Kansas City, Kans.) Following palliative operation a patient with proven carcinoma of the ampulla has been known to live 33 months, after transduodenal resection patients have lived 4 to 22 years, and after resection of the duodenum and head of the pancreas one patient has lived 34 months, although the average length of life in each of these groups is much shorter. The average time of survival of patients with carcinoma of the ampullary region is shown in Table I. The results of the radical operation, as shown in this table, justify the procedure, without question.

The mortality of the palliative operation has been recorded by Collier and Winfield as low as 26+ per cent, and by Lieber, Stewart and Lund as high as 78+ per cent.

TABLE I
AVERAGE LENGTH OF LIFE

Without treatment (Outerbridge)	7 3 mos
With palliative operation (Judd and Parker)	7 7 mos
With radium and roentgen ray treatment (Pack and McNeer)	8 0 mos
With radical operation (Hunt's review) 30 cases dead	1 7+ yrs
With radical operation (Hunt's review) 34 cases still living last report	2 5+ yrs

The average mortality of the radical operation in the cases collected by Hunt was 30+ per cent. With present methods of controlling the bleeding tendency in jaundice and treating liver damage, the operative mortality of excision of ampullary tumors should soon compare favorably with operations upon the stomach and rectum for carcinoma.

The choice of the transduodenal or Whipple operation should depend upon the extent of the lesion found at operation. With the recorded excellent results of the former technic we must assume that the more radical procedure is not necessary when the tumor is small and confined to the ampulla. However the Whipple technic more nearly fulfills the requirements of an operation for carcinoma, in that the region of early extension of the tumor is removed. Carcinoma arising in the pancreas and involving the common duct or ampulla is suitable only for the Whipple operation.

The percentage of carcinomata involving the ampulla or ampullary region which are suitable for radical excision is not yet known. The total number of these tumors as compared to carcinomata in the remainder of the pancreas is also not known. In a recent study of 52 cases of proven carcinoma of the pancreas and ampullary region, 17 or 32 per cent were found in the latter group (Schnedorf and Orr). This is a small number but probably indicates the approximate percentage of tumors arising in the ampulla as compared to tumors having their origin in the pancreas.

The remote effect of excision of a portion or all of the head of the pancreas without reimplantation of the pancreatic duct into the intestine has not yet been studied. Experimental work by Dragstedt indicates that sclerosis of the pancreas may result, followed by fatty infiltration of the liver due to the loss of the hormone lipocin. A careful study of necropsy material will decide this point in the future.

In order to obtain relatively accurate statistical records of patients operated upon, supplementary reports must be made indicating the length of life after operation. In the series reviewed by Doctor Hunt, more than one-third of the cases have no recorded final report.

Below is a follow-up report of one case and a brief record of a new case. Both of these patients were operated upon by the Whipple technic.

Case 1—My first case which was reported at a meeting of the Western Surgical Association in December, 1940 is still alive 11½ mos after the second stage of the operation. On April 6, 1941, he was operated upon for complete obstruction of the ileum due to a band of adhesions. He still has a small fistula from his jejunum which intermittently opens and discharges for a few days. There is no evidence of pancreatic fistula.

Case 2—M. C. B., female, age 67, was admitted to the University of Kansas Hospital, November 16, 1940. The history and findings were those of carcinoma of the ampulla. A cholecystogastrostomy and gastro-enterostomy were performed November 23, 1940. A very stormy convalescence followed, and after 49 days she was sent home to recuperate.

This patient was readmitted to the Hospital, March 10, 1941, and the second stage of the Whipple operation was performed, March 24, 1941. The duodenum and entire head of the pancreas were resected. The pathologist's report of the tumor removed was "ulcerating adenocarcinoma of the ampulla of Vater with extension into the head of the pancreas and regional lymph nodes."

An uncomplicated postoperative recovery was made and the wound was completely healed within 16 days.

FIFTY-TWO PROVEN CASES OF CARCINOMA OF THE PANCREAS AND THE AMPULLA OF VATER WITH SPECIAL REFERENCE TO FATTY INFILTRATION OF THE LIVER

J G SCHNEDORF, M D , P H D ,

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CANCER OF THE PANCREAS constitutes about 1 to 2 per cent of all malignancies Ewing¹ states that it was found in 1.76 per cent of Kaufmann's autopsies on malignant tumors, and in 2 per cent of Korte's autopsies on 2,943 cases of cancer He states that Bashford collected 1,000 cases of carcinoma of the pancreas in 84,000 cancers

The analysis of 40 autopsies by D'Aunoy, Odgen and Halpert² indicates a grave prognosis and rapidly fatal outcome of the disease In 38 of the 40 patients, the clinical course of the illness lasted one to eight months, with an average duration of four and one-half months A similar hopeless outlook is expressed by Lahey and MacKinnon³ in their analysis of 47 cases, and by Kauer and Glenn⁴ in their study of 32 cases

In 1935, Whipple, Paisons, and Mullins⁵ reported the successful resection of the duodenum and a portion of the pancreas for carcinoma involving the ampulla of Vater and the head of the pancreas Since that date, 14 cases have been reported in the literature and one of us (T G O⁶) has just reported the fifteenth case This patient is alive and well eight months after the resection Whipple⁷ reported one patient who was alive and well, with a gain of 30 pounds in weight, two years after the original operation

In 1934, Hunt and Budd⁸ collected 76 cases of radical extirpation of carcinoma involving the perampullary region, with an operative mortality of 38 per cent They estimated that 85 such cases had been recorded, but they were unable to accurately verify this estimate From 1925 to 1934, these authors found recorded cases of transduodenal excision which lived three, five, and eight years after operation, respectively Thus, radical resection has altered the rapidly fatal outcome of the disease when it has been treated in its early stages

Renewed interest in this problem has led us to review the cases which appear in the records of the University of Kansas Hospitals during the past 20 years In addition to 35 cases of primary carcinoma of the pancreas, 17 cases of carcinoma of the ampullary region were also reviewed because of the similarity of symptoms produced and because in their early stages they are amenable to similar surgical treatment Only those cases proven by autopsy or surgical biopsy are included in this analysis

CARCINOMA OF THE PANCREAS

Incidence—Carcinoma of the pancreas is a condition found most frequently in the fifth and sixth decades of life. All our patients were between ages 46 and 78. Three patients were in their late forties, 13 in their fifties, 15 in their sixties, and four were in their seventies. Thirty-two of the patients were white and three were colored. Other series reported by D'Aunoy, *et al* (40 autopsy cases), Lahey and MacKinnon (47 cases), and Grauer⁹ (34 autopsy cases), also indicate that the disease occurs anywhere from ages 26 to 80, but that it is most frequent in the fifth and sixth decades of life. Although primary carcinoma of the pancreas is exceedingly rare in persons under 20 years of age, the literature contains reports of about nine proven cases. Mielcarek¹⁰ collected five proven cases from the literature up to 1935. The youngest was an infant age 7 months. He reported the sixth case which occurred in a boy age 15. He listed five other cases from the literature as doubtful because they lacked proof. Since then, Smith¹¹ reported one case in a boy age 14½, Jeanneney and Laporte¹² one case in a girl age 17, and Kaletchek¹³ a case in a girl age 14. The ratio of incidence in the male and female varied from 17:1 in D'Aunoy's series to 23:24 in Lahey's series.

Pathology—In almost all of our cases, the tumor was hard and scirrhous. In two instances, a soft medullary tumor was found. The tumors arose from the acini in the majority of the patients. In five cases, definite indication that it arose from pancreatic duct epithelium was found. In 25 cases, the tumor involved the head, in seven, the body, and in three cases, the whole pancreas was involved in an extensive growth.

Symptoms—The symptoms complained of were mild and of recent duration at the time that the patients presented themselves at the hospital. The duration of the symptoms varied from one to nine months. Only five patients complained of vague abdominal symptoms of two to five years' duration. The most frequent complaints were vague abdominal discomfort, indigestion, gas, and dyspepsia. Rapid weight loss and weakness were complaints in 85 per cent of the cases. Jaundice was present in 17 of 23 cases of cancer of the head of the pancreas, and was reported as being present in 22 of 31 patients in D'Aunoy's series. In two cases, the jaundice was intermittent while in 15, it was severe and progressive. Jaundice was not present in any of the cases of carcinoma of the body of the pancreas. Symptoms of duodenal obstruction occurred in seven instances and duodenal ulceration in three. Gas was one of the chief complaints in 15 patients, absent in five, and not complained of by the other 15 patients. In the majority of cases, pain was mild and vague in character. In 16 patients, it was localized to the mid-epigastrium, in three, to the right upper quadrant, in two, to the back only, and in four, to the epigastric region and back, and in one case, to the right shoulder blade. The pain was severe and sharp in only two cases. In one case it was severe and colicky. The colicky pain in the latter patient probably came from the biliary passages because he also had an intermittent jaundice. Pain was not complained of by two patients. This is in contrast to the

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conclusion of Kauer and Glenn, who found that pain was the most common chief complaint in 68 per cent of their patients. The pain in the patients with carcinoma of the body of the pancreas did not differ in severity from that of the head of the pancreas. Archibald and Kaufman¹⁴ describe the pain in carcinoma of the body of the pancreas as being extremely severe and destroying in character in contrast to the vague pain in carcinoma of the head and tail of the pancreas. In their analysis of 19 cases of primary carcinoma of the body and tail of the pancreas, Levy and Lichtman¹⁵ report a wide variation in the reference and type of pain complained of. Occasionally, it would simulate gallbladder disease or penetrating ulcer but it was unrelated to the digestive cycle.

A palpable abdominal tumor was found in 23 of our 35 cases. In ten patients, it was located in the region of the gallbladder, in eight, it was mid-epigastric, in two, it was at the umbilicus, and in three, it was felt in the left epigastric region. In the latter three cases, the tumor involved the body of the gland. Ascites was present in three patients.

Twenty-seven of the patients were explored and palliative operations were performed. Cholecystogastrostomy was performed in six cases, and cholecystostomy in one case, to relieve biliary obstruction. Gastro-enterostomy was performed in six cases, and duodenojejunoscopy in one case, to relieve duodenal obstruction.

Early, extensive metastases were observed to be the rule. These were noted at the time of operation and at autopsy. Metastases involved the adjacent lymph nodes, liver, and lungs. Extension of the growth by contiguity to the mesentery, peritoneum, and adjacent organs was frequent.

Mortality—Carcinoma of the pancreas was a rapidly fatal condition in our patients. The duration of symptoms was short in the majority of the patients and varied from one to nine months. In all of our patients, death occurred two to ten months after the onset of symptoms, and from two and one-half to five months after the onset of progressive jaundice. All of the patients upon whom palliative operation was resorted to for relief of biliary or duodenal obstruction died within five weeks after the operation. D'Aunoy, *et al*, reported the duration of illness in 38 of their 40 cases to be one to eight months, with an average of four and one-half months.

CARCINOMA OF THE AMPULLA OF VATER

We have reviewed 17 proven cases of carcinoma of the ampullary region. Three of the lesions were fungative and had undergone mucoid degeneration. Ten of the patients were men and seven were women. Three were in their forties, four in their fifties, seven in their sixties, and three in their seventies.

The symptoms were mild and were present two to 15 months at the time of admission, with an average duration of four months. Vague epigastric discomfort, nausea, vomiting, anorexia, weakness, and rapid loss of weight were the chief symptoms. Progressive jaundice unassociated with severe

pain was present in all patients. A palpable, right upper quadrant mass was felt in four patients.

Operation was performed in 16 instances. Biopsy only was done in four cases, cholecystogastriostomy was performed in six patients, cholecystectomy in one, and cholecystoduodenostomy in one patient. This latter patient lived 33 months after cholecystoduodenostomy for an obstructive lesion of the ampulla. A hard nodule in the head of the pancreas was felt at operation but no biopsy was obtained. Autopsy after death showed an adenocarcinoma of the ampulla of Vater. It is entirely possible, but not likely, that this patient had a benign obstruction which was relieved by operation and that he subsequently developed an ampullary malignancy. Choledochogastriostomy and resection of the head of the pancreas and duodenum was performed in one patient. This patient is still alive and in good condition, eight months after operation. The average duration of life from the onset of the symptoms was five months (two to nine months). The growths extended up into the bile ducts, to the pancreas and duodenum, and metastasized to the liver, lungs, and ovaries.

Fatty Infiltration and Degeneration of the Liver—Eight of our 35 cases of carcinoma showed definite fatty metamorphosis of the liver at autopsy. A brief summary of the individual cases is charted in Table I.

TABLE I
FATTY INFILTRATION AND DEGENERATION OF THE LIVER IN PATIENTS WITH
CARCINOMA OF THE PANCREAS AND AMPULLARY REGION

Case No	Age	Sex	Duration of Symptoms (Mos)	Duration of Jaundice (Mos)	Location of Carcinoma	Changes in the Pancreas
1	57	M	5	3	Head	Generalized atrophy of pancreas Chronic pancreatitis
2	51	F	1	1	Head	Chronic fibrous pancreatitis
3	62	M	4	0	Body	Extensive carcinoma of body of pancreas
4	59	M	8	0	Head	Extensive carcinoma of head of pancreas
5	57	F	5	0	Body	Chronic interstitial pancreatitis
6	61	M	2	2	Head	
7	75	F	9	0	Head	Chronic pancreatitis
8	71	M	6	0	Head	Fibrosis of pancreas
9	60	M	15	3	Ampulla	Chronic pancreatitis
10	55	M	6	1½	Ampulla	Chronic cystic pancreatitis

The rôle of the pancreas in controlling the endogenous metabolism of fat, particularly in the liver, was suggested by early experiments upon dogs. In 1924, Fisher,¹⁶ and also Allan, Bowie, MacLeod and Robinson¹⁷ reported that life could be maintained in totally pancreatectomized dogs for only one to 11 months, even though the blood sugar was controlled by daily administration of insulin. At death, the greatest change was observed in the liver. There was marked fatty infiltration and degeneration. The fat content of the liver increased to 39.5 per cent. These observations were subsequently confirmed in experiments on dogs by Hershey¹⁸ (1930).

Conflicting experimental evidence is found in the literature as to whether fatty metamorphosis of the liver can be produced by loss of pancreatic secretion through total pancreatic fistula and by ligation of the pancreatic ducts. In 1931, Beig and Zucker,¹⁹ and Hershey reported the development of fatty livers in dogs following the loss of pancreatic juice by total external pancreatic fistula in from 17 to 56 days. Excessive fatty infiltration of the liver also occurred after prolonged obstruction of the pancreatic ducts (80 days) by ligation. Van Plohaska, Dragstedt, and Harms²⁰ found fatty livers in three of their seven dogs with pancreatic fistula, but ascribed this occurrence to intercurrent infection which developed in these three dogs. Two had a subcutaneous abscess, and one died from peritonitis. The other four dogs had normal livers. Two of their three dogs with ligated pancreatic ducts showed fatty livers, the third did not. In spite of these observations, they concluded that fatty degeneration of the liver does not occur in dogs with total pancreatic fistula and in dogs with ligated pancreatic ducts. Boyce and McFetridge²¹ present evidence which indicates that fatty changes in the liver develop after complete or partial pancreatectomy but do not occur when the pancreatic ducts are severed and ligated with the pancreas left *in situ*. Ralli, Rubin, and Present²² repeated these experiments on dogs in 1938, in an attempt to clarify this controversy. They found that careful ligation of the pancreatic ducts and separation of the pancreas from the intestine in three dogs produced fatty changes in the livers which were indistinguishable from those of pancreatectomized dogs.

Thus, some investigators maintain that their evidence indicates that the external secretion of the pancreas contains the factor necessary for the control of fat metabolism in the liver. Others do not agree with this contention. Feeding of pancreatic juice and administration of extracts of pancreatic juice did not prevent or cure the fatty changes in the experiments of Van Plohaska, *et al*, and of Dragstedt.²⁴ One hundred grams of raw pancreas added to the daily diet was effective in preventing the fatty degeneration. Hershey found that substitution of 10 Gm of lecithin for raw pancreas in the daily diet also maintained normal liver fat. Best, Ferguson, and Hershey²³ found that adding choline to the diet in amounts equal to that present in 10 Gm of lecithin protected the animal. This indicated that the active principle in lecithin is choline. Dragstedt summarized the results of three years' investigation of the problem in 1940. He pointed out that 100 Gm of raw pancreas fed daily is effective in protecting the liver and that it contains only 250 mg of choline, whereas 2 Gm of choline a day or more is necessary. He also states that the lecithin in the raw pancreas is specific. Feeding liver or brain which contains a lot more lecithin and choline exerts no beneficial effect. He has prepared an active alcohol soluble extract of beef pancreas 60 to 100 mg of which are effective by mouth and subcutaneously. The extract is free from fat and contains only 1 to 2 per cent choline. He concludes that this substance is specific and active in small amounts, and is not choline, but a new pancreatic hormone which he has termed "lipocaic."

The foregoing experimental evidence indicates that the pancreas is concerned with the endogenous metabolism of fat in the liver. Fatty infiltration and degeneration of the liver occurs following total pancreatectomy, and also may follow a loss of pancreatic juice in total fistula and following ligation of the pancreatic ducts. This fatty metamorphosis of the liver can be prevented in the dog by feeding raw pancreas (100 Gm daily), and, according to some workers, lecithin (10 Gm daily), choline (2 Gm daily), and lipocaic (60 to 100 mg daily). The fact that fatty liver follows ligation of the pancreatic ducts in some instances does not mean that it is due to a loss of pancreatic juice. It may well be due to a decrease in lipocaic below the maintenance level, because of fibrosis of the pancreas and degeneration of lipocaic producing parenchyma. The same may be true following chronic pancreatitis and fibrosis in the case of total pancreatic fistula. Cole²⁵ has called attention to fatty infiltration of the liver associated with pancreatic fibrosis. Snell and Comfort²⁶ report cases of pancreatic lithiasis and atrophy as probable causes of fatty changes in the liver. Our ten cases show that fatty infiltration and degeneration of the liver can occur with pancreatic insufficiency due to cancer involvement of the pancreas. In most of the cases presented, the carcinoma involved the ducts and produced obstruction, secondary atrophy, and chronic inflammation of the pancreas. In some instances, most of the gland was replaced by cancer. If fatty metamorphosis of the liver is due to extensive functional destruction of the pancreas, one might expect to have an associated diabetes. None of our patients had glycosuria or hyperglycemia. Reports of infrequent cases of diabetes with cancer of the pancreas have been recorded by Uhry,²⁷ and by Pygott and Osborn.²⁸ Apparently, in our patients protection against fatty metamorphosis of the liver required more pancreatic tissue than was needed to prevent diabetes. On the other hand, the fatty infiltration of the liver observed in our patients may be due to a loss of the external pancreatic secretion due to obstruction of the pancreatic ducts, as occurred in the dogs of Berg, *et al*, Van Prohaska, *et al*, and Ralli, *et al*. Regardless of the mechanism involved, experimental evidence and the presence of fatty livers in ten of our patients warrants the administration of lecithin (10 Gm daily), choline (2 Gm daily) or lipocaic (100 mg daily) to patients with pancreatic insufficiency, both preoperatively and postoperatively.

The rapidly fatal course of the disease in our series, and in the other series reported in the literature, does not offer much hope for patients with carcinoma of the pancreas or ampullary region. The few successful resections reported within the past seven years bring some hope if the lesion is discovered early. In most instances, however, patients do not seek medical help until jaundice or marked loss of weight has occurred, during which time extensive metastases have already developed, so that death follows shortly after they are seen.

An early diagnosis may be hoped for in the future by a thorough investigation of the pancreas in all cases of inexplicable abdominal pain, rapid

weight loss, nausea, and jaundice. Stools should be analyzed for their fat after several days of a standard diet of known fat content. Samples of duodenal juice should be obtained by intubation and analyzed for pancreatic ferments. Blood amylase and lipase, which are elevated in obstructions of the pancreatic ducts, may be suggestive. Carcinoma of the body or tail of the pancreas may not produce any detectable loss of the external secretion of the gland. In many cases, the pain may also be vague and mild so that early diagnosis is extremely difficult or impossible without operation. Gastroscopic examination may be of some diagnostic value but only after the tumor has grown to a large size. Moersch and Comfort²⁹ report gastroscopic examination in two cases of carcinoma of the body of the pancreas in which the tumor caused a bulging of the stomach wall, which could not be obliterated by inflation of the stomach with air.

An exploratory operation is justified even in advanced cases. In early lesions involving the ampulla and head of the pancreas, radical resection is the procedure which gives the only hope of cure to the patient. In advanced cases, palliative operations for relief of biliary or duodenal obstruction are indicated to increase the comfort of the patient during the last stages of the disease. In spite of the fact that all of our patients, except one, died within five weeks of the palliative operation, such treatment is indicated because in some instances the patient's life may be greatly prolonged, as shown by our case noted above of a man age 60 who lived 33 months after palliative cholecystoduodenostomy for carcinoma of the head of the pancreas. This case was confirmed at autopsy. Coughlin and McCaughan³¹ also report prolonged survivals in three patients following cholecysto-enterostomy for tumor of the head of the pancreas, one was alive at three months, one at 14 months, and one at five years, respectively.

CONCLUSIONS

(1) An analysis of the problem of carcinoma of the pancreas and ampullary region is made from a study of 52 patients, with a proven diagnosis by autopsy or biopsy.

(2) The rapidly fatal course of the disease, in most of the patients, is pointed out.

(3) Thorough investigation of pancreatic function is advisable for the diagnosis of an early obscure cancer of the pancreas or ampulla of Vater in all cases of inexplicable abdominal complaints.

(4) Radical resection, by the technic of Whipple or that of Hunt and Budd, offers the only hope for cure of early carcinoma of the ampullary region or the head of the pancreas. Palliative operation for relief of biliary or duodenal obstruction, even in advanced cases is indicated, not only to make the patient more comfortable but to prolong life.

(5) Fatty infiltration and degeneration of the liver was found at autopsy in ten of our 52 patients with carcinoma of the ampulla and head of the pancreas. We have tried to explain this on the basis of the experimental

evidence found in the literature, which is reviewed. The feeding of lecithin, choline, pancreatic extract, or lipocaine is indicated in the preoperative and postoperative treatment of these patients to prevent fatty changes in the liver and to maintain life.

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THE RATIONALE OF RADICAL SURGERY FOR CANCER OF THE PANCREAS AND AMPULLARY REGION¹

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UNTIL 1935, pancreaticoduodenectomy for cancer involving the pancreas was not attempted for the following reasons (1) The duodenum was believed to be an essential part of the digestive tract (2) The external secretion of the pancreas was believed to be indispensable for digestion of proteins and fats (3) The significance of the fact that pancreatic juice ceases to flow and that acinar atrophy results with prolonged blockage of the ampulla and head of the pancreas with carcinoma was not properly understood or evaluated (4) For these reasons, even with resections of part of the duodenum, every effort was made to reestablish the flow of bile and pancreatic juice into the duodenum or jejunum

Halsted,¹ in 1898, was the first to carry out such an operation successfully Doctor Hunt has summarized the collected cases of this type, some 110 in the literature and by personal communication Because the unsuccessful operations have not been reported, the results are somewhat misleading in evaluating the collected cases, both as to operative mortality and the late results

Nevertheless, for carcinoma limited to the papilla of Vater, transduodenal resection with reimplantation of the common and pancreatic duct into the duodenum offers definite advantages and this is especially true of the fungating or papillary type of carcinoma of the ampulla

But not all cancers of the ampulla are of the fungating type, nor are all of the fungating growths relatively benign Many of them infiltrate either the pancreas or the common duct, or the duodenum Attempts to excise a segment of the head of the pancreas, wide of the growth, with a reimplantation of the ducts or head of the pancreas into the duodenum or jejunum have, in many instances, been associated with fatal hemorrhage, peritonitis, or duodenal fistula This is especially true if catgut is used for ligatures and sutures The activated pancreatic juice rapidly digests catgut Surgeons, in the past, have hesitated to use silk or cotton because they considered the duodenum a contaminated field

Following the fatal outcome, due to duodenal fistula and peritonitis, in a transduodenal excision of an ampullary carcinoma which I performed in 1935, we decided to undertake a more radical operation in two stages for the following reasons (1) Coffey,² in 1909, and Mann and Kawamura,³ in 1922, had demonstrated that the dog could survive total duodenectomy (2) Patients with ampullary or pancreatic cancer were able to survive for months

* Discussion of Dr Verne Hunt's paper read at the meeting of the American Surgical Association, White Sulphur Springs, W Va, April 28, 1941

TABLE I
 FORTY-ONE COLLECTED CASES OF RADICAL PANCREATICODUODENECTOMY FOR CARCINOMA
(Collected from the Literature and from Personal Communications)
 To April 15, 1941

Operator	Reported in Journal	Stage	Ampul- lary	Pan- creas	Duo- denum	Com- mon Duct	Died Post oper	Died After Opera- tion	Surviv- ing	C ₁ with Metas- tases	Recur- rence	Fus- tula Post- oper
1 Parsons	ANNALS OF SURGERY, 102, 763 1935	2	✓					9 mos		✓		Biliary Pneumatic Pneumatic
2 Whipple	ANNALS OF SURGERY 102, 763, 1935	2	✓	✓				28 mos		✓		
3 Whipple	Amer Jour Surg 40, n s 260 1938	2		✓				5 mos				
4 Schullinger-Parsons	Amer Jour Surg 40, n s, 260 1938	2		✓								
5 Janssen-Whipple	Amer Jour Surg 40 n s 260 1938	2		✓								
6 Whipple	Not reported	2 ¹		✓			✓					Biliary Pneumatic Pneumatic
7 Whipple	Not reported	2 ¹		✓			✓	15 mos				
8 Whipple	Not reported	1		✓			✓	15 mos				
9 Whipple	Not reported	1		✓			✓					
10 Trout	Personal communication	1			✓		✓					
11 Jones	Personal communication	2	✓				✓					
12 Jones	Personal communication	2					✓	2 mos				
13 Hollenberg	Personal communication	2			✓			35 mos				
14 Orator	Zentralblatt f Chr 64, No 25 1936	2	✓					5 mos				Biliary Pneumatic
15 Crile Jr	Amer Jour Surg, Jan 1940	-		✓				18 mos		✓		Pneumatic Biliary
16 Zimnunger	Personal communication	2 ¹	✓					17 mos				Pneumatic Biliary
17 Zimnunger	Personal communication	2 ¹	✓					4 mos				
18 Zimnunger	Personal communication	1		✓				3 mos				
19 Watt	Personal communication	2		✓			✓	5 wks				
20 Illingworth	Edinburgh Med Jour 46, 331 1939	2		✓								
21 Powers	Personal communication	2		✓				3 mos				
22 Trimble	Personal communication	1		✓				11 mos				
23 Luke	Personal communication	2	✓	✓				15 mos				
24 Pfeiffer	Personal communication	2		✓	✓			6 wks				
25 Horsley	In print ANNALS OF SURGERY 1941	1	✓				✓					
26 Jones	Personal communication (Crile)	2		✓				5 mos				
27 Freeman	Personal communication	2	✓					5 mos				
28 Freeman	Personal communication	2	✓					11 mos				Pneumatic Biliary
29 Freeman	Personal communication	2	✓					1 mo				
30 Fallon	Personal communication	2				✓		6 mos				
31 Fallon	Personal communication	2		✓								
32 Fallon	Personal communication	2 ¹		✓			✓					Biliary
33 Fallon	Personal communication	1		✓	✓			2 mos				
34 Brunschwig	Surg Gynec and Obstet 65, 681, 1937	2		✓			✓					
35 Brunschwig	Personal communication	2				✓		3 mos				
36 Brunschwig	Personal communication	2		✓			✓					Pneumatic Pneumatic
37 Roscher	Norsk Mag f Laegevid 98, 777 1937	2	✓				✓	5 mos				
38 Ransom	Personal communication (Hunt)	2	✓									
39 Orr	Tr West Surg Assn 1940	2	✓					7 mos				
40 Hunt	Personal communication	1	✓					1 yr				
41 Hunt	Personal communication	2	✓									

¹ A modified two-stage procedure

RÉSUMÉ OF MORTALITY INCIDENCE
FOLLOWING RADICAL OPERATIONS FOR CARCINOMA, WITH RESECTION OF
DUODENUM AND PANCREAS

Collected Cases to April 15 1941

	Two Stage	Postop Deaths	One Stage	Postop Deaths
Carcinoma of ampulla	16	2	4	2
Carcinoma of pancreas	14	7	2	0
Carcinoma of duodenum	2	1	1	0
Carcinoma of common duct	2	0	—	—
Totals	34	10	7	2
Total operated cases	41			
Postoperative deaths	12			
Operative mortality	29.2%			

deprived of both biliary and pancreatic contents in the gastro-intestinal tract, and showed an atrophy of disuse of the acinar tissue of the pancreas (3) If bile could be restored by a short-circuiting procedure the bleeding tendency would be corrected and digestion of fat improved. At the same operation a gastro-enterostomy would prepare the patient for the second stage, at which time radical removal of the duodenum and head of the pancreas, wide of the growth, would be undertaken.

Doctor Pansons and I¹ operated upon the first patient, employing the two-stage procedure, in 1935. At the second stage, a partial duodenectomy with excision of part of the head of the pancreas, with duodenoduodenostomy, but with exclusion of the pancreas from the digestive tract, was accomplished. In the second case I¹ performed a total duodenectomy, with excision of a part of the head of the pancreas. The patient lived 28 months, but died of liver metastases. Both of these patients digested 80 to 85 per cent of a measured fat intake, on several determinations. But both of them developed cholangitis because of the cholecystogastrostomy.

Because of the tendency for infectious material to be pushed into the gall-bladder and the development of a stenosis of the stoma with biliary infection, we² modified the short-circuiting procedure in the first stage to an end-to-end cholecystojejunostomy, with an end-to-side jejunojejunostomy. In some 31 such operations (the great majority of them palliative), we have found a very low incidence of cholangitis, and now strongly advise it as a first-stage procedure, rather than a cholecystogastrostomy.

But the two-stage procedure, as reported in the literature, and in personal communications to me by surgeons who know of my interest in the subject, carries with it certain hazards and complications which must be eliminated if the radical operation is to be considered worth while. The two most serious complications are postoperative bile and pancreatic fistula. In the 41 collected cases, there have occurred five bile and eight pancreatic fistulae (Table I). The former seldom close spontaneously, the latter usually do. The bile fistula is due to the cutting through of the silk or linen ligature used in tying off the common duct in the second stage. If possible, it is, undoubtedly, better

policy to implant the end of the common duct into the jejunum. Pancreatic fistula can be avoided by ligating the dilated pancreatic ducts before approximating the cut surfaces of the V-shaped excision in the head or body of the pancreas.

Now that we can prepare jaundiced patients for operations with vitamin K and bile salts, and can prevent shock by adequate measures, it is possible, in early and in selected cases, to undertake the radical operation in one stage. This avoids the hazard of two anesthetics and two major procedures.

I performed the first successful one-stage radical pancreaticoduodenectomy in March, 1940, removing the distal third of the stomach, the entire duodenum, and the head of the pancreas with an antecolic gastrojejunostomy and a choledochojejunostomy. This 47-year-old woman has regained 20 pounds, and is now living and free from any signs of jaundice or recurrence, 14 months after operation. The second patient upon whom I performed a similar one-stage procedure, in September, 1940, died of a postoperative pneumonia on the fourth day.

Fine silk technic should be used in all pancreatic surgery. Some of these patients will show a poor fat digestion, others good digestion. We are carrying out a series of experiments to explain this discrepancy. Pancreatic extract should be given to those who show fat indigestion. In our patients who have died following the radical two-stage procedure, we have not found fatty liver degeneration. However, it may be wise to give these patients lipocain after operation.

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ANASTOMOSIS OF THE BILE DUCTS TO THE GASTRO-INTESTINAL TRACT BY A METHOD OF TRANSFIXION NECROSING SUTURE*

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ANASTOMOSIS between the bile ducts and the gastro-intestinal tract may results in cicatricial stenosis of the stoma,[†] with resulting increase of intra-ductal pressure, stasis of the bile, dilatation of the biliary tree and ascending infection of the ducts and liver,^{††} with resulting liver damage. A large stoma at the site of anastomosis frequently results in regurgitation into the biliary system^{††} of pancreatic juice, food and bacteria with resulting liver damage, as evidenced by liver enlargement,^{††} dilatation of the bile ducts, liver necrosis and infection. The immediate mortality and late results of the performance of such an anastomosis depend also on the damage to the liver at the time of operation,^{††} the biliary ductal segment available for use, as well as upon the difficulty and uncertainty of the anastomosis performed.¹¹⁶

Whipple,¹²⁰ in 1928, stated that "the rare successes not the many failures appear in the literature." Evarts Graham,¹⁶ in 1938, stated that "almost invariably the patient succumbs from multiple abscesses in the liver if the anastomosis remains open." Arthur Allen,¹ in 1940, stated that "one wishes to avoid, if possible, anastomosis between the duct and the gastro-intestinal tract, since under these circumstances an ascending infection is so apt to occur." Waltman Walters,¹¹⁶ in 1939, stated that "life has been prolonged by operation to 25 per cent of the normal expectation."

The principles involved in the selection of a site in the gastro-intestinal tract for anastomosis to the biliary system concern themselves with the accessibility and motility of the duodenum,[†] the low potential of infection in the stomach, which is somewhat modified by the gross character of its contents and its anatomic disparity,^{††} and the universal motility of the jejunum.^{68, 123} During exposure of the duct,¹¹⁶ preservation of the peritoneum^{††} periductal tissues, nerve and blood supply of the duct is important.

* Read before the American Surgical Association, White Sulphur Springs, W Va, April 28-30, 1941

[†] References in this group are 17, 24, 30, 59, 66, 70, 80, 84, 86, 90, 96, 104, 107, 116, 118, 119, 122, 123

^{††} References in this group are 1, 31, 43, 60, 62, 63, 65, 66, 69, 89, 104, 119, 121

^{††} References in this group are 9, 14, 15, 29, 31, 44, 55, 70, 81, 98, 108, 112, 123

^{††} References in this group are 70, 99, 109, 123

^{††} References in this group are 86, 111, 116, 123

^{††} References in this group are 59, 73, 123

^{††} References in this group are 10, 47, 59, 70, 73, 102, 123

^{††} References in this group are 18, 75, 89

The reported methods and cases of cholangio-enterostomy are numerous ^{1†} Gaston,³⁰ in 1885, reported anastomosis between the gallbladder and duodenum by a suture, as follows² "Sufficient inflammation ensued from a single stitch of silk thread to unite the walls, while it cut an opening between these cavities which closed in five months in one dog, but in this the common duct had not been ligated below. No obstruction or infection in the biliary tree, the viscera had not had an inflammation propagated from the suture to the attached walls." Gage³⁷ found histopathologic changes in all of 40 normal dog livers, which consisted of round cell infiltration, small areas of necrosis, and small abscess-like areas, after choledochoduodenostomy, 46.6 per cent showed increase in the pathologic changes after 15 days. Sandblom, Beigh, and Ivy¹⁰¹ stated that "the site of anastomosis does not affect the problem of ascending liver infection." These authors anastomosed the gallbladder to the duodenum after pyloric exclusion and ascending liver infection occurred. Gentile⁴² found that ascending liver infection occurred after gastric resection and cholecystogastrostomy.

Bernhard¹⁴ reported the finding of roentgenologic evidence of regurgitation of stomach contents into the liver after anastomosis between the gallbladder and gastro-intestinal tract. Ellsworth Eliot³¹ stated that "the fear of infectious cholangitis has been dissipated by the instances of barium, introduced into the stomach, which has been found to penetrate the hepatic tributaries with no indication of even mild cholangitis."

Mallet-Guy,⁷⁰ in 1940, stated that "in the dog, after choledochoduodenostomy, pancreatic reflux often causes liver necrosis. The presence of air in the biliary tree is common and the incidence of barium reflux is great." McWhorter⁸¹ reported a case seven years after hepaticoduodenostomy, with liver enlargement, in which barium regurgitated into the biliary tree. Wildergans¹²³ observed that there had been numerous cases in which barium was evident in the branches of the hepatic duct after choledochoduodenostomy.

Beaver and Mann,¹² Beig,⁷ Coffey,²⁵ Walton,¹¹⁸ and perhaps others, placed the end of the common bile duct into the lumen of the duodenum and found universal dilatation of the biliary tree. Bachrach and Fogelson⁹ found that when the common duct was pulled into the lumen of the jejunum through a stab wound and anchored to the distal wall, seven out of 13 animals lived for two to two and three-quarter years, there was regurgitation of barium in one and moderate ductal dilatation with negligible pathologic changes in the liver. These authors also found that bile peritonitis and later common duct obstruction followed when the common duct was fastened to the jejunum by sutures and the jejunal wall invaginated about the duct with a purse-string.

Anastomosis between the bile ducts and the gastro-intestinal tract in which transplanted tissues are used result in cicatricial stenosis, as shown by Horsley.⁵³ Anastomosis by suturing the duct and gastro-intestinal tract over

^{††} References in this group are 9, 12, 16, 24, 25, 31, 32, 35, 36, 38, 39, 45, 48, 49, 50, 52, 53, 58, 59, 65, 67, 69, 70, 71, 74, 76, 78, 79, 80, 83, 84, 88, 92, 99, 102, 104, 105, 106, 111, 116, 120, 123, 125.

a rubber tube, or the use of a rubber tube to bridge a gap between the two, was performed by Brewer,²¹ Cahen,²¹ Fowler,¹⁵ Mayo⁷⁵ Jackson,⁵⁸ Mallet-Guy,⁷⁰ and Lahey,⁶⁷ with relatively poor results due to recurrence of stricture when the tube was removed and obstruction secondary to encrustations about the tube. Lahey stated that "the large majority of cases with rubber tubes have attacks of chills, jaundice and fever." McArthur⁷⁹ used a tube with a cuff on the duodenal end and reported satisfactory late results in five cases.

A direct suture was first performed by Mayo⁷⁵ in two cases. Guerry⁵⁰ reported seven cases, with satisfactory results in four. Judd⁶² anastomosed the hepatic duct to the duodenum by direct suture in 47 cases, there was contracture of the anastomosis in seven, after one to six months, also in another paper, Judd and Burden⁶¹ reported 13 anastomoses of this type with 15 per cent failures. Ladd and Gross⁶⁵ reported nine cases well after five to 16 years, these were instances of congenital stricture and atresia of the biliary tract. These authors stated "successful issue depends on care of doing anastomosis, it is not necessary to form a valve-like submucous transplantation. The mucous membrane of the duct and stomach or duodenum must be accurately opposed and no stenosis must exist." Eliot,³¹ in 1936, collected, from the literature, 56 cases of hepaticoduodenostomy, and found 11 well after ten to 20 years. This author stated that "cholangitis is a frequent complication." Walters,¹¹⁶ in 1939, reported 61 per cent of 80 operated cases of benign strictures of the common and hepatic duct anastomoses to the gastro-intestinal tract were performed, and 68 per cent obtained good results.

An external biliary fistula was transplanted to the gastro-intestinal tract in 41 cases collected by Eliot,³¹ and five good results recorded. Contracture of the biliary fistula was found to be common. Lahey⁶⁷ stated that "several failures were due to repeated attacks of cholangitis."

Operative Procedure—The principal feature of the method is the anastomosis of the bile duct to the gastro-intestinal mucosa by the necrosing effect of a No. 6 plain silk transfixion suture put through the ductal wall and gastro-intestinal mucosa (Fig. 1). The serosa and musculature of the gastro-intestinal tract are incised down to the submucosa. A medial or posterior row of mattress sutures which evert the edge of the gastro-intestinal incision around the duct are introduced through the peritoneum and connective tissue medial to the duct (Fig. 2). The transfixion suture is introduced into the duct for a distance equal to about two times the diameter of the normal duct, and the same length into the lumen of the gastro-intestinal tract. The duct wall and gastro-intestinal mucosa are crushed under pressure, by tying the transfixion suture. The operation is completed by suturing the everted anterior edge of the gastro-intestinal incision to the tissues lateral to the wall of the duct which places the duct in a covered submucous position in relation to the gastro-intestinal tract. This technic was employed in the experiments as well as the following variation. Figure 3 shows how, in the majority of the experiments, the sutures between the edges of the gastro-intestinal incision and the periductal tissues are introduced under the duct. In introducing these

sutures at the most superior portions of the duct and the gastro-intestinal tract, the tissues at the side of the duct are employed for suturing, in order to avoid constriction of the duct (Fig 4) The completion of the operation is similar to that shown in Figure 2

Results—Anastomosis between the common bile duct and the gastro-intestinal tract was performed by this technic upon 55 dogs Deaths before

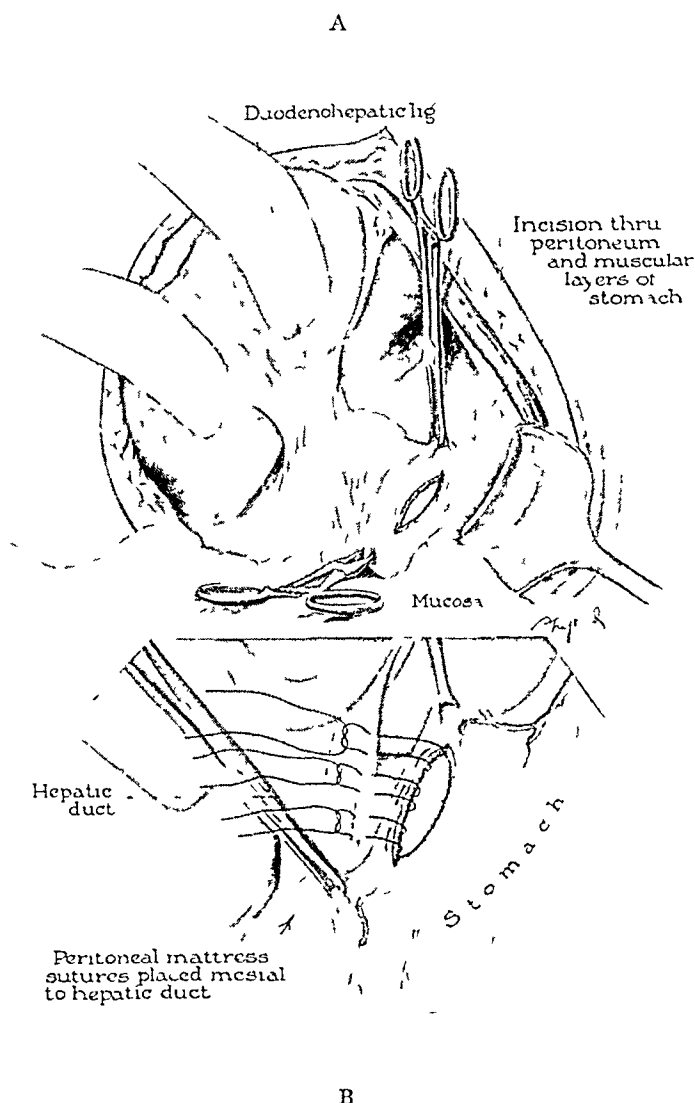


FIG 1—Anastomosis between the extrahepatic bile ducts and the stomach, in which technic the sutures between the duct and stomach do not pass under the bile duct (A) Showing the duodeno-hepatic ligament pylorus and distal end of the stomach on the lesser curvature of which an incision has been made through the serosa and musculature layers (B) Showing the bile duct lying beneath the peritoneum mattress sutures between the undermined edge of the incision and the periductal tissue lateral to the duct are started on the serosal side of the stomach and the stomach and duct are approximated Figure 2 shows the completed operation

18 days were caused by pneumonia, in 12, jaundice, in 9, evisceration, in 3, leakage of anastomosis, in 2, rupture of hepatic duct, in 1, sponge under the liver, in 2 and causes unrelated to operation, in 2

(A) *Effect of Type of Necrosing Suture*—Anastomoses, using a silk transfexion necrosing suture was established 38 times in 34 dogs (Figs 5 and 6) living over seven days, with three exceptions which will be discussed later

Four anastomoses using catgut, one using a strand of doubled silk, and one using heavy serum-proofed silk were not established

(B) *Effect of Removal of the Peritoneum from the Bile Duct*—Two simultaneous anastomoses (Fig 7), of 1 cm each, in six dogs, one through peritonealized duct and one through deperitonealized duct, resulted in all, through a peritonealized duct being established, and three, because of a deper-

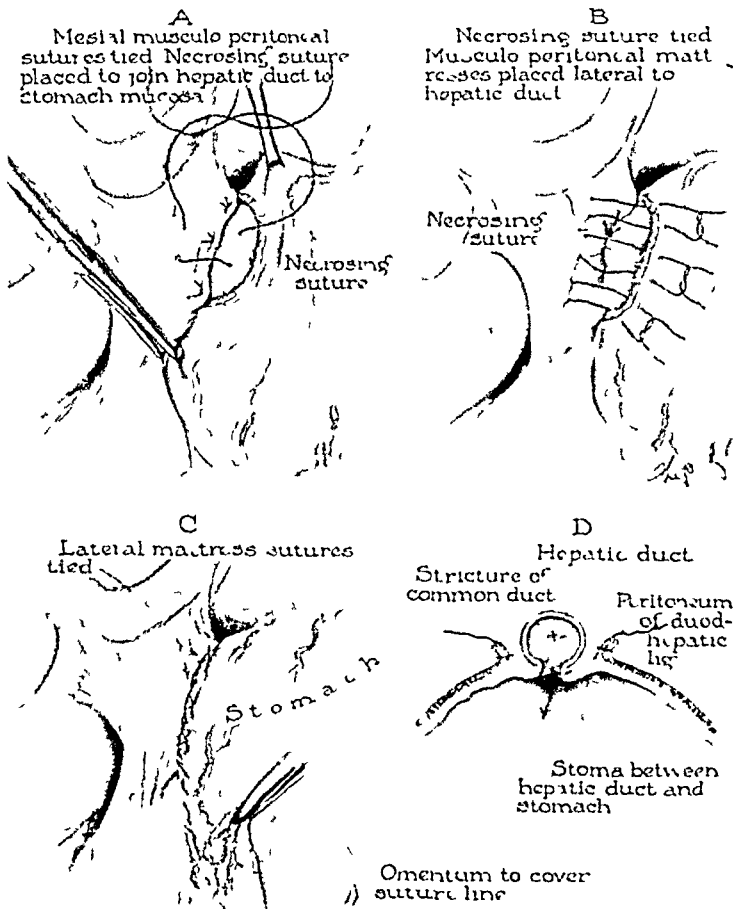


Fig 2—Continuation of anastomosis between the bile duct and the stomach (see Fig 1) (A) Curved cutting needle on silk transfixion suture has been passed into the bile duct longitudinally, and into the lumen of the stomach through the gastric mucosa parallel to and equal in length to that in the bile duct the posterior row of sutures (Fig 1) has been tied (B) T lateral edge of the duct and the posterior edge of the gastric incision (B) T pressure and the musculo-peritoneal mattress sutures placed are started on the gastric serosa, thus everting the undermined edge around the duct (C) Lateral mattress sutures tied thus covering the duct and gastric mucosa containing the transfixion necrosing suture, operation may be completed by suturing omentum over the suture line (D) Sectional view showing bile duct in the wall of the stomach peritoneum of the duodenohepatic ligament, looking distally down the bile duct toward the obstructive stricture in the duct and the anastomotic stoma between the bile duct and the stomach. This technic was employed in some of the experiments reported and is less difficult to perform, both choledochoduodenostomy and choledochogastrostomy were performed in this way

itonealized duct, failing to be established. These are the three failures mentioned previously.

(C) *Effect of Size of Anastomosis*—An anastomosis of 1 cm in eight dogs resulted in universal dilatation of ducts and regurgitation of intestinal contents with liver necrosis in 2, and liver abscess in 1. The anastomosis

BILIARY-INTESTINAL ANASTOMOSIS

was 3 to 7 Mm after one to 13 months Deaths were due to pneumonia, in 3, emaciation, 2, liver abscess, 1, infected wound, 1, and one was sacrificed The results are shown in the upper part of Table I

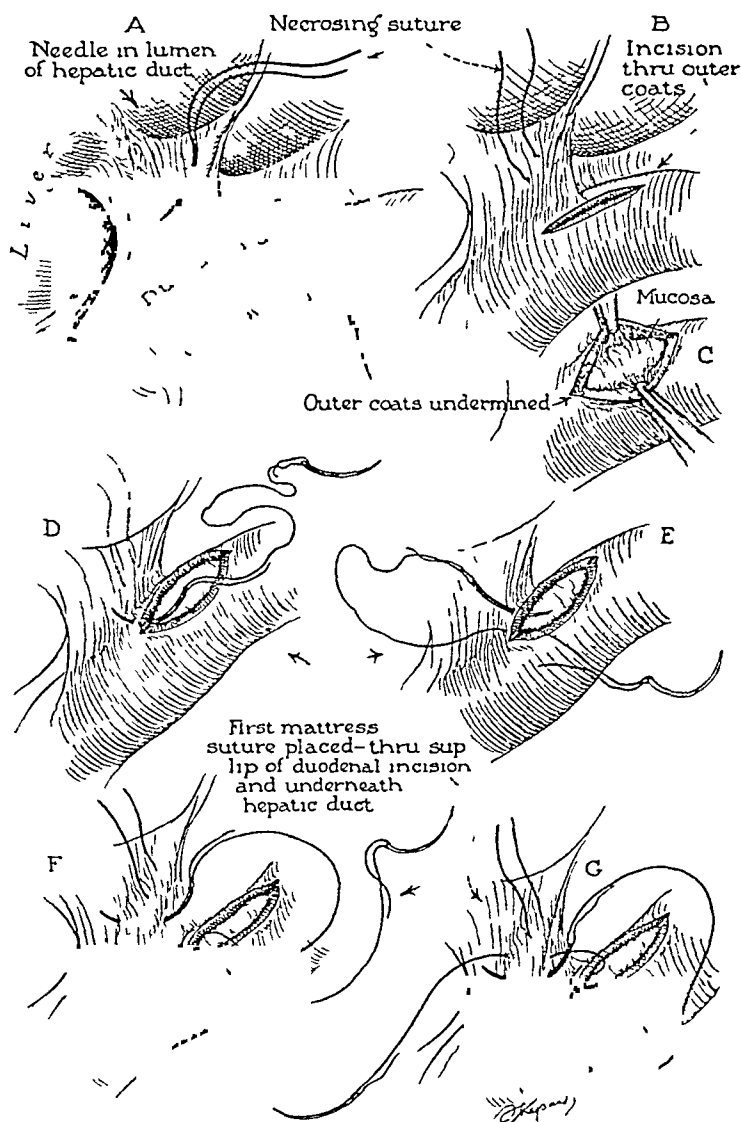


FIG 3—Anastomosis between the extrahepatic bile ducts and the duodenum (A) Curved needle on silk transfexion necrosing suture has been placed into the lumen of the bile duct and out, producing a suture longitudinally in the duct, including duct wall and peritoneum overlying the duct (B) Longitudinal incision through serosa and muscle of the duodenum (C) Edges of incision undermined (D E, F G) Showing insertion of mattress suture between the edge of incision and the region of the bile duct, suture is started on the serosal side to invert the incision around the duct these sutures pass under the duct Figure 4 shows completion of the anastomosis

An anastomosis of 0.5 cm in 13 animals resulted in the absence of pathologic changes in all, excepting ductal dilatation in 2, and slight liver necrosis in 1 The anastomosis was 5 to 3 Mm after one to nine months Deaths were due to pneumonia, in 4, hepatic failure, 1, and 7 were sacrificed The results are shown in the lower part of Table I

(D) *Effect of Immediate Section of the Common Duct Below the Anastomosis*—The common bile duct was immediately sectioned below the anastomosis measuring 0.5 cm in 23 dogs In ten, living 18 days to nine months, this resulted in the absence of pathologic changes in all, excepting one showing

regurgitation and slight liver necrosis. Early deaths, before 18 days, were caused by pneumonia, in 10, jaundice, in 1, rupture of hepatic duct, in 1, and infected wound, in 1. Late deaths, 18 days to nine months, were caused by pneumonia, in 2, infected wound, 1, and 7 were sacrificed (Figs 8 and 9).

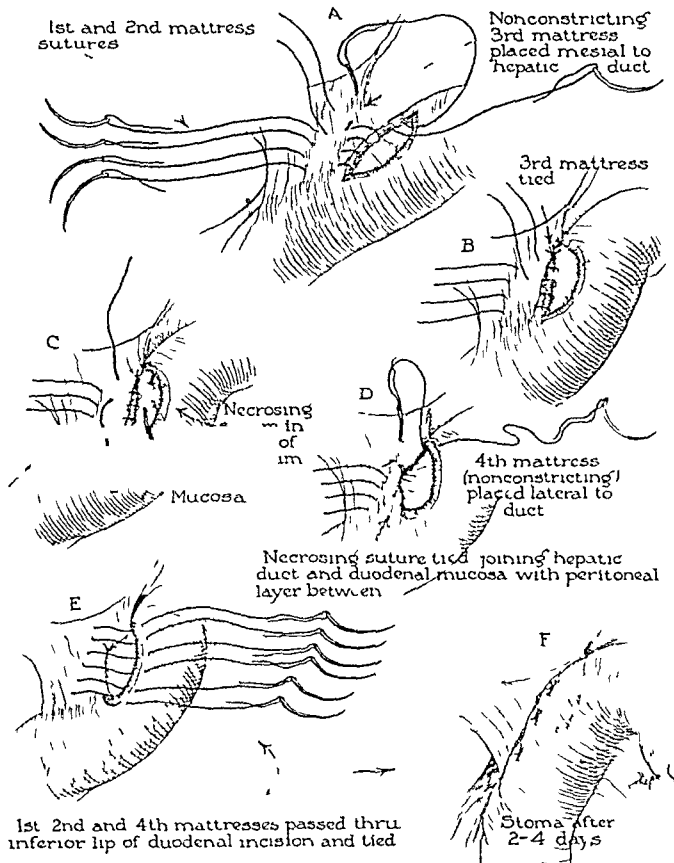


FIG. 4—Continuation of anastomosis between the extrahepatic bile duct and the duodenum. (A) First mattress suture (Fig. 3) and second have been placed; the third (B) is between the incision edge and the periductal tissue medial to the duct, to avoid stricture of the duct by the suture. (C) The transfixion necrosing suture which was placed into the duct (Fig. 3 A) has been put on a curved cutting needle and passed into and out of the lumen of the duodenum catching the duodenal mucosa parallel to and equal to the length of suture already in the ductal wall. (D) The nonconstricting third mattress suture has been tied, approximating the duodenal incision and the medial side of the duct. (E) A suture similar to that shown in (A) is placed to approximate the upper part of outside edge of incision to lateral wall of bile duct. (F) Anastomosis is completed by passing the sutures through the free duodenal edge tying and thus covering the duct and transfixion necrosing suture which has been tied under pressure. (G) Completed operation showing submucosal position of bile duct and the immobilization of the duodenum and the approximate position of the stoma. This technic was employed in most of the experiments reported, both in anastomosis between the stomach and bile duct and between the duodenum and bile duct.

(E) *Effect of Site of Anastomosis in the Gastro-Intestinal Tract*—An anastomosis of 0.5 cm between the common bile duct and duodenum in ten animals resulted in absence of pathologic changes in all, except regurgitation and slight liver necrosis in one. The anastomosis was 5 to 3 Mm after one to nine months.

An anastomosis of 0.5 cm between the common bile duct and the stomach in three dogs, living one to three months, resulted in absence of pathologic

changes in all. The anastomosis was 3 Mm (Fig 10)

(F) *Effect of Type of Gastro-Intestinal Incision*—A transverse gastro-intestinal incision was made in connection with the anastomoses of 0.5 cm in three animals, living 18 days to five months, and resulted in liver necrosis and regurgitation in one.

A longitudinal gastro-intestinal incision was made in connection with the anastomoses of 0.5 cm in 13 animals, living one to nine months, and resulted in the absence of pathologic changes in all (Fig 11)



FIG 5—A photomicrograph of a cross section of anastomosis between the common bile duct and the duodenum, taken 48 hours after operation. Necrosis of the ductal wall and duodenal mucosa, indicated by arrow, has occurred demonstrating the early establishment of choledochoduodenostomy, to be compared to illustration (D) of Figure 2

TABLE I

GROUP I ANASTOMOSES OF ONE CENTIMETER					
No	Mos	Anastomosis	Regurgitation	Ductal Dilatation	Liver
9	1	5 Mm	Positive	2 times	Normal
12	2	4 Mm	Positive	4 times	Normal
7	3	6 Mm	Positive	3 times	Necrosis
6	4	7 Mm	Positive	2 times	Normal
2	4	5 Mm	Positive	4 times	Abscess
5	6	6 Mm	Positive	1 times	Necrosis
11	8	4 Mm	Positive	1 times	Normal
1	13	3 Mm	Negative	4 times	Normal
GROUP II ANASTOMOSES OF ONE HALF CENTIMETER					
13	1	5 Mm	Negative	Negative	Normal
40	1	3 Mm	Negative	Negative	Normal
55	1	3 Mm	Negative	Negative	Normal
45	2	3 Mm	Negative	Negative	Normal
35	2	4 Mm	Negative	Negative	Normal
48	3	3 Mm	Negative	Negative	Normal
44	4	4 Mm	Negative	Negative	Normal
39	5	3 Mm	Negative	Negative	Normal
33	5	5 Mm	Negative	Negative	Normal
25	5	3 Mm	Negative	Negative	Normal
15	5	3 Mm	Positive	2 times	Necrosis
16	8	3 Mm	Negative	Negative	Normal
32	9	3 Mm	Negative	2 times	Normal

(G) *Effect of Removal of Gallbladder Together with Section of the Common Duct*—The gallbladder was removed simultaneously with section of the common duct and the performance of an anastomosis of 0.5 cm in three animals, living five to eight months, resulted in the absence of pathologic changes, in 2, and regurgitation and slight liver necrosis in 1. The anastomosis was 3 Mm (Fig 12)

Preoperative cultures of gallbladder bile in 21 dogs resulted in three positive cultures. Postoperative cultures of gallbladder bile and of the liver in six dogs, one to nine months after anastomosis, resulted in all positive

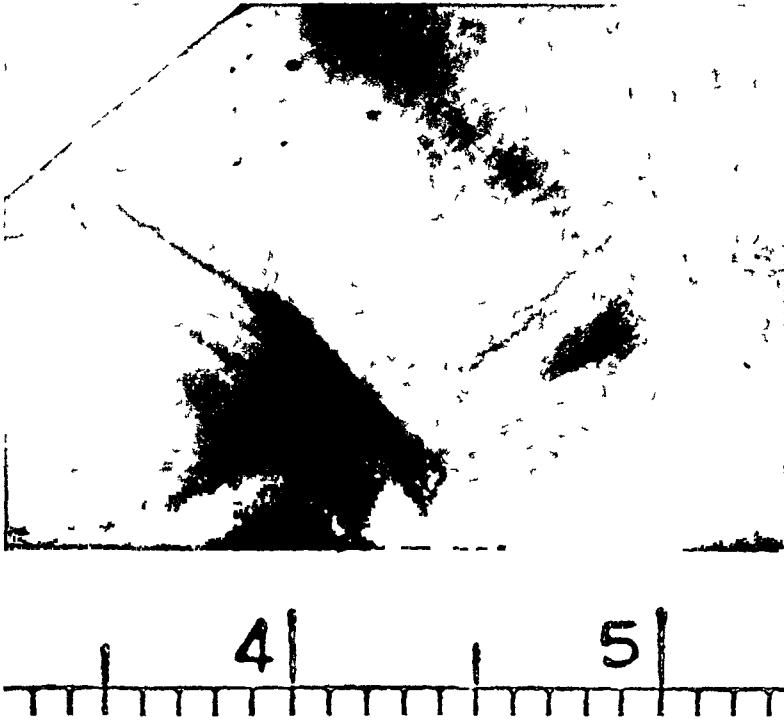


FIG 6—A photograph of duodenal mucosa at the site of choledochoduodenostomy 13 months after operation. The anastomotic opening measured three millimeters in diameter and was protected by a fold of duodenal mucosa. The common duct was sectioned distal to the anastomosis one month after choledochoduodenostomy was performed.

cultures. This suggests that anastomotic openings between the bile ducts and gastro-intestinal tract results in the presence of bacteria in the bile.

CONCLUSIONS

(1) In the anastomosis of the bile ducts to the gastro-intestinal tract the size of the anastomosis appears to be important.

The necrosing suture must include a bite of tissue about two times the diameter of the normal duct, which results in an opening slightly larger than the diameter of the duct. This results in a lack of stenosis of the stoma which is, on the other hand, small enough to prevent regurgitation of gross contents of the gastro-intestinal tract. If the necrosing suture is made to produce an opening two or three times the diam-

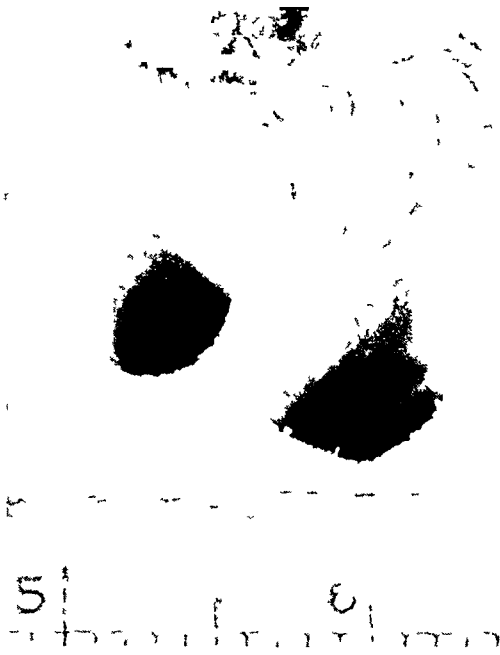


FIG 7—A photograph of a double choledochoduodenostomy from the duodenal side nine months after operation. The anastomosis on the left was performed after deperitonealization of the duct and measured three millimeters in diameter while on the right the duct remained peritonealized and the opening measured five millimeters in diameter.

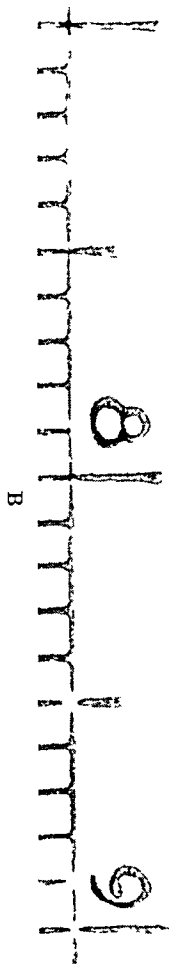


Fig. 8—(A) Photograph of fresh specimen of liver, bile ducts, duodenum and anastomosis, five months after operation (B) Photograph of magnification of the fresh duodenal mucosa showing the anastomotic opening, which was oval, and measured three millimeters in diameter

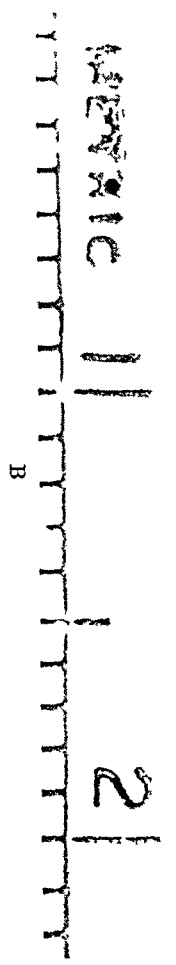


Fig. 9—(A) Photograph of fresh specimen, nine months after operation, in which choledochoduodenostomy was performed, and the common duct remained in continuity to the ampulla, the bile ducts are dilated (B) Photograph of the anastomosis, after fixing in formalin, which measured three millimeters in diameter

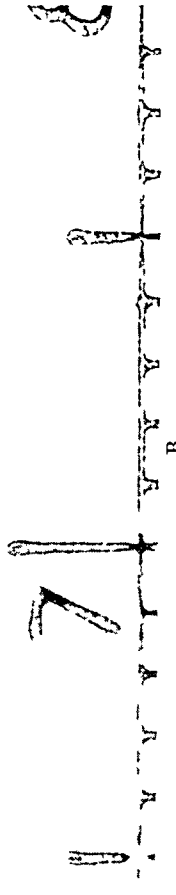
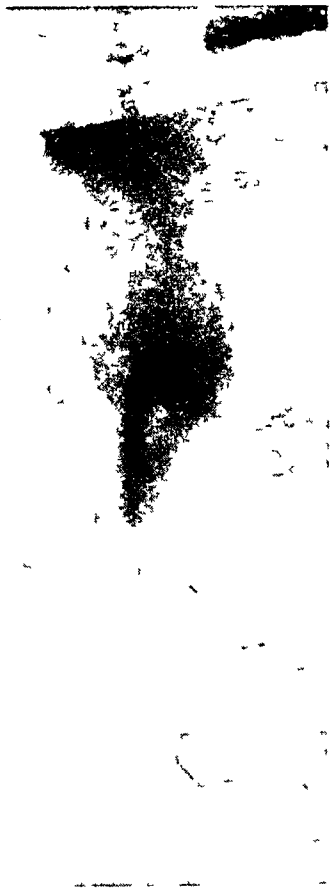
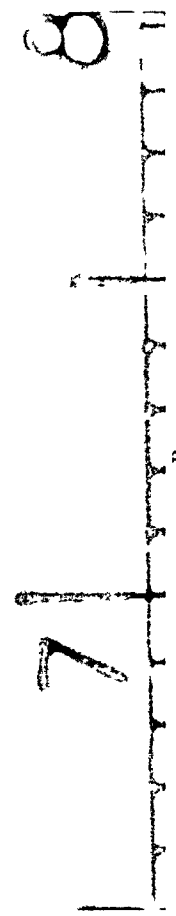
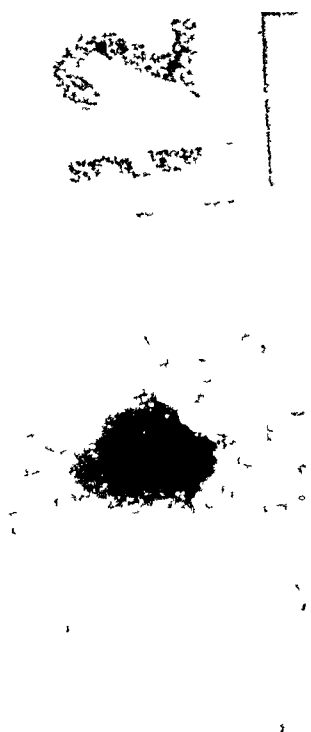


FIG 11—(A) Photograph of liver, gallbladder bile duct, and duodenal wall, with anastomosis performed by making a longitudinal incision in the duodenal wall, after four months. (B) Photograph of anastomosis after fixing in formalin which measured four millimeters and was located three centimeters distal to the pylorus.

FIG 10—(A) Photograph of fresh specimen of liver gallbladder and stomach wall, with anastomosis, three months after operation. (B) Photograph of anastomosis, after fixing in formalin which measured four millimeters in diameter.

eter of the normal duct, regurgitation of gross particles of gastro-intestinal contents is common, and dilatation of the ducts, and infection of the liver occurs

(2) This method of transfixion necrosing suture appears to be a simple procedure to attain this objective, and is more controllable than a direct layer-suture

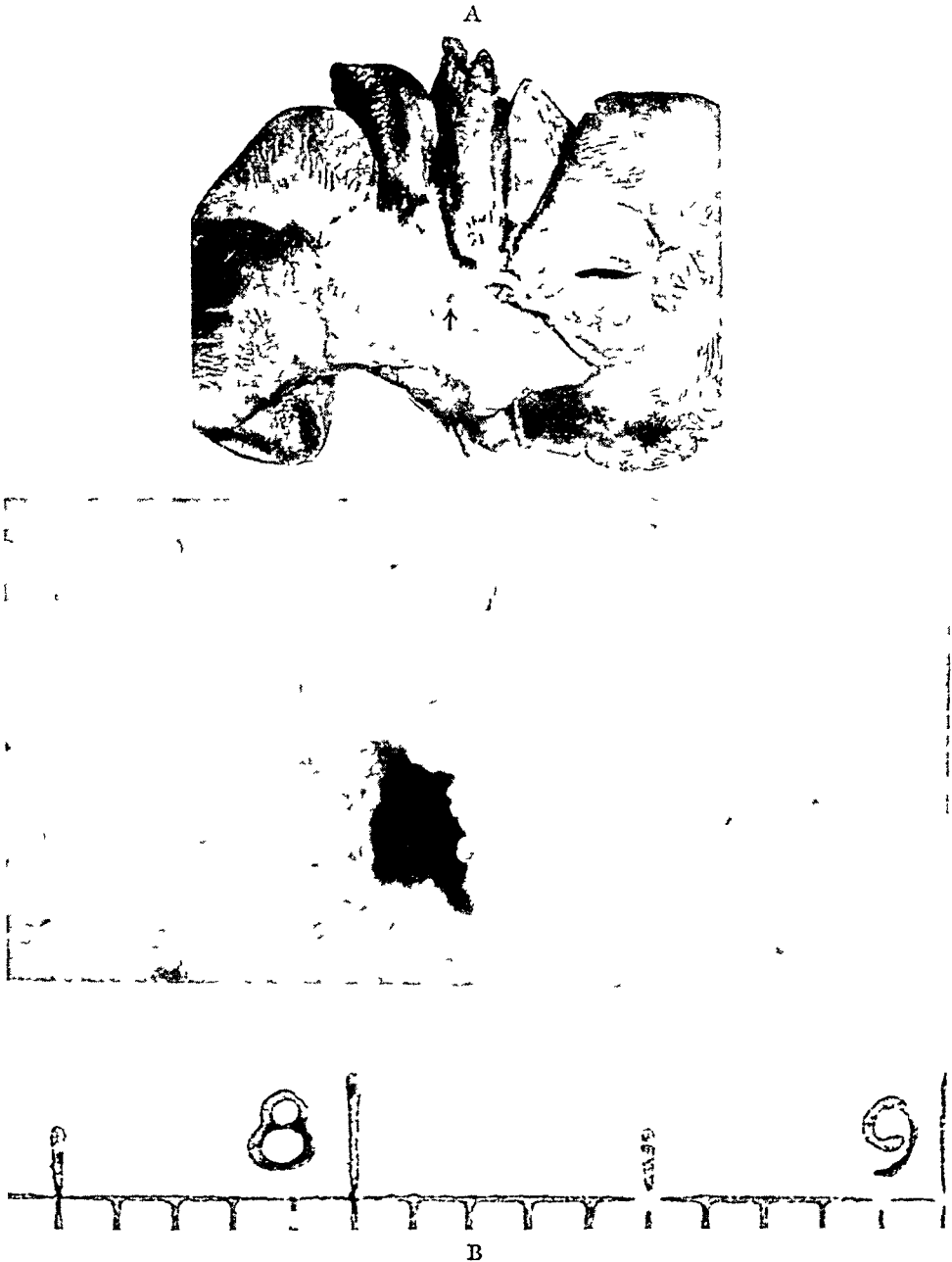


FIG. 12 —(A) Photograph of fresh specimen of liver common bile duct and duodenal wall with the anastomosis, shown five months after operation (B) Photograph of anastomosis, after fixing in formalin which measured 3 x 5 Mm

(3) As a transfixion suture a single silk ligature is the best material, and it should always be employed on peritonealized duct which insures proper adherence of the peritoneal surfaces of the duct and the gastro-intestinal tract

(4) A silk transfixion necrosing suture for anastomosis between the bile ducts and the gastro-intestinal tract was efficient in 38 anastomoses in 34

dogs It failed in three, where the duct was deperitonealized In other words, it is a reliable method to produce a controlled size of anastomosis Its adoption on experimental findings is debatable, but it is an easily performed anastomosis between the bile ducts and the gastro-intestinal tract, and facilitates the operation where the layer-suture procedure is very difficult to perform

(5) No conclusion could be reached about the most desirable site in the gastro-intestinal tract for anastomosis, except that lack of tension is very important—longitudinal incision through the serosa and the muscle of the gastro-intestinal tract seems desirable

(6) A silk transfixion necrosing suture requires from two to four days to cut through, and, if carried out in the presence of complete obstructive jaundice, external biliary drainage should be temporarily beneficial

Assistance in illustrations was rendered by G W Reis, M W Praddock, and the Photography Department of Rush Medical College

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DISCUSSION.—DR WAITMAN WAITERS (Rochester, Minn.) Doctors Brackin and David have applied this method of transfixion suture necrosis anastomosis to the technic of anastomosis between the common bile duct or gallbladder and the duodenum or the stomach, which Doctor Coffey was first to describe in the anastomosis of the ureter to the intestine.

Two years ago Doctor Brackin presented his experimental studies on ureterosigmoidal anastomosis, and emphasized at that time, as he did again to-day, the fact that when the peritoneum was allowed to remain in contact with the ureter (and in contact with the common bile duct in the experiments of this year), a more satisfactory anastomosis occurred without the degree of contraction which otherwise resulted when the peritoneum was deflected.

It seems to me that, as Doctor Brackin brought out in his concluding statement, a sufficient period will have to elapse after application of this principle to biliary-intestinal anastomosis for patients before one can arrive at a definite decision that it is superior to the direct method of anastomosis which we all know.

I am very much interested in Doctor Brackin's report of his results in three cases in which the method had been employed in ureterosigmoidal transplantation. One of these patients now has lived more than 24 months, and has been without evidence of obstruction at the anastomosis, or without evidence of renal infection.

I think the experiments have been well conceived and well carried out. I am not convinced that the method is a superior one in the matter of reduction in the amount of infection in the biliary tract subsequent to its use, in comparison to those cases in which direct anastomosis is used. Furthermore, I never have been thoroughly convinced that a method which is dependent on factors over which the surgeon does not have complete control—and by that I mean transfixion suture necrosis anastomosis—is superior to the direct method of anastomosis.

I should like, also, to call attention to the fact that with the deeply jaundiced patient, where this method of anastomosis is used, in that period of danger, namely, the 48 hours subsequent to operation, in which bleeding is likely to occur and hepatic and renal insufficiency may take place, the great safeguard against those possibilities of bleeding and of the development of hepatic insufficiency immediately after operation is immediate relief of the obstruction. I am sure it has been the experience of all surgeons in operations upon deeply jaundiced patients, that those who fail to recover usually are those whose obstruction has not been completely relieved, and whereas the patient may not have had evidence of bleeding or hepatic or renal insufficiency prior to operation, it may develop immediately subsequent to operation.

Furthermore, I am not convinced that anastomosis of the gallbladder to the stomach or duodenum may not have superior advantages when it is done for the human being over those of anastomosis of common bile duct, remembering, of course, that mention was made of the application of this method to anastomosis of the gallbladder as well as the common bile duct.

In such cases, it seems worthy of emphasis that among human beings, when direct anastomosis of the gallbladder is made to the stomach or duodenum, contrary to these experimental results, a larger anastomosis is preferable to a smaller one, the reason probably being that in the smaller anastomosis edema occurs at the site of the anastomosis, interfering with relief of the obstruction, with bleeding and hepatic insufficiency possibly occurring subsequently.

I think the method is worthy of trial in suitable cases, and I think that it may demonstrate some advantages over the direct method. I should like to suggest to Doctor Brackin that further study might be worth while in determining the relative relationship between intragastric or intraduodenal pressure and intrabiliary pressure among human beings in comparison to such pressures in experimental animals.

I believe the reason that intrahepatic infection develops among so few patients subsequent to cholecysto-enterostomy is that the liver has sufficient natural capacity to withstand infection which undoubtedly occurs, in contrast to the situation in the experimental animal, but in addition, I believe there is a possibility that when complete obstruction is present in the human being the amount of secretory pressure in the biliary tract is sufficient to prevent the fluid in the stomach or duodenum from regurgitating into the extrahepatic biliary tree, even though some of it might reach the gallbladder. In the case of the gallbladder, as was brought out this afternoon, there probably is associated some mechanism

concerned with the emptying or filling of the gallbladder around the valves of Heister, which might exert a protective influence when foreign fluids enter the gallbladder

DR THOMAS H LANMAN (Boston) I was very much interested in hearing the two last speakers I want to speak of some experiences we have had at the Boston Children's Hospital in treating congenital anomalies of the bile ducts

We agree with Doctor Walters, that direct anastomosis seems to serve better than any other method, and we are not at all afraid of having a large stoma in these small patients The results, as we have followed them for eight or ten years, are most satisfactory, and we have been impressed not only with the relief of symptoms but with the very great power of liver regeneration that these young patients exhibit, once the obstructive jaundice is relieved These patients are usually operated upon at one to two months of age All of them have had no communication between the liver and gastrointestinal tract We feel that the direct anastomosis is, if possible, more satisfactory in this type of young patient

DR VERNON C DAVID (Chicago, Ill, closing) I agree with Doctors Walters and Lanman, that in most obstructions, where the gallbladder is still present, the direct anastomosis, by suture of the gallbladder into the gastro-intestinal tract, is a very satisfactory and proper means of anastomosis My particular interest in this method was stimulated by the difficult cases, where the gallbladder has been taken out, where the ducts are difficult to find, and where the mechanical problem of making a layer of anastomosis between the common duct and the gastro-intestinal tract presents a real problem

One such instance I should like to relate briefly, where the principle of necrosing suture was employed A patient, operated upon elsewhere for gallstones had, following her operation, a rapidly deepening jaundice, she was told by her surgeon that an anomaly of the ducts had been present, so that it was necessary to insert a tube in part of the ductile system to convey the bile The jaundice persisted, and was accompanied by the usual picture of sepsis, chills, and fever

Two years after this occurrence, the patient being deeply jaundiced, coming to this country, we explored her and found that a red rubber tube had taken the place of part of the common duct and lay in scar tissue very close to the liver After removal of this tube, the only portion of the duct that I was able to find, was an opening in the liver on the same plane as the liver, and the distal end of the common duct we were not able to identify

Under these conditions, we attempted to repair by the use of the transfixion, necrosing silk suture introduced through the duodenum, on the basis that while we knew we would have bile leakage around the anastomosis, the approximation of the peritoneum of the liver and the duodenum would agglutinate, to some degree, these two organs, so that, as the necrosing suture cut through, the bile drainage could be reestablished through the hepatic duct into the duodenum Therefore, the duodenum was sutured posteriorly to the hepatic duct on Glisson's capsule and a necrosing suture was put through the duodenal wall, then the duodenum sutured anterior to the duct This patient drained bile four or five days, and then began to show bile in the intestinal tract and has had normal bile drainage since It is too short a period to say how permanent this new anastomosis will be, and how little fraught with danger it may be, but at any rate, here the principle was used, to our great satisfaction, in creating a new stoma, the size of which could be controlled fairly accurately by the necrosing suture in the duodenum

It seems to me that it is in these cases that the method is useful, and it appeals to me because it allows the surgeon to predicate, fairly accurately, the size of the anastomosis as well as to greatly simplify the technic where the going is difficult

ASEPTIC, IMMEDIATE ANASTOMOSIS FOLLOWING RESECTION OF THE COLON FOR CARCINOMA *

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THE HISTORY of the surgical treatment of cancer of the colon parallels the history of surgical progress in overcoming the hazards of infection. The general principles for the treatment of malignancy anywhere apply in cancer of the colon. The primary tumor must be widely excised in one block with the tributary lymphatic channels and nodes, but in cancer of the colon this surgical procedure must be carried out upon an organ the lumen of which is teeming with bacteria. Peritonitis was, and still is, one of the chief causes of mortality following operation. The early operations upon cancer of the colon were performed in the era of antiseptic surgery and the mortality was very high. In other fields of surgery the hazards of infection declined with the development of asepsis, but in operations upon the colon it has been far more difficult to solve the problem of avoiding contamination of the peritoneal cavity, and of the wound in the abdominal wall. DeBovis,⁷ in 1900, and more recently Rankin¹⁶ and Cope⁷ have published excellent histories of the early surgical procedures employed in carcinoma of the colon. We shall only mention a few points of interest in the more recent developments.

At an early date surgeons began to concern themselves with developing methods for removing the malignant lesion and at the same time avoiding fatal infections. Thomas Bryant,¹ in 1882, was the first surgeon to report the successful removal of a carcinoma of the colon by pulling the growth outside the abdominal wall and suturing the limbs of the bowel to the abdominal incision, thus avoiding contamination of the peritoneal cavity. Barton,² of Philadelphia, in 1888, also reported the successful removal of a carcinoma of the colon by an extra-abdominal resection. The growth which was at the ileocecal valve was withdrawn from the abdomen, cut off, and an enterotome was immediately applied to crush the spur between the ileum and the ascending colon. The abdominal wound was closed around the limbs of the bowel which was brought out of the abdomen. Bloch,⁴ of Copenhagen, also reported a successful result by this method in 1892. Paul,²⁹ in 1895, published his classic article describing his experience with seven patients, which, he said, "represents the education of an individual surgeon." His technic changed from one of immediate anastomosis to the safer procedure of freeing the growth sufficiently to draw it outside the abdomen. The descending and ascending limbs of the bowel attached to the tumor were sutured together, the growth and the adjacent portions of the bowel were cut

* Read before the American Surgical Association, White Sulphur Springs, W. Va., April 28-30, 1941.

off, and glass tubes tied into the projecting limbs of the colon (Fig 1) The spur was later crushed with a Dupuytren's clamp, and still later the colostomy was closed by a plastic procedure, without entering the peritoneal cavity A somewhat similar procedure was adopted by Mikulicz²³ However, he did not suture together the limbs of the bowel protruding from the abdomen In

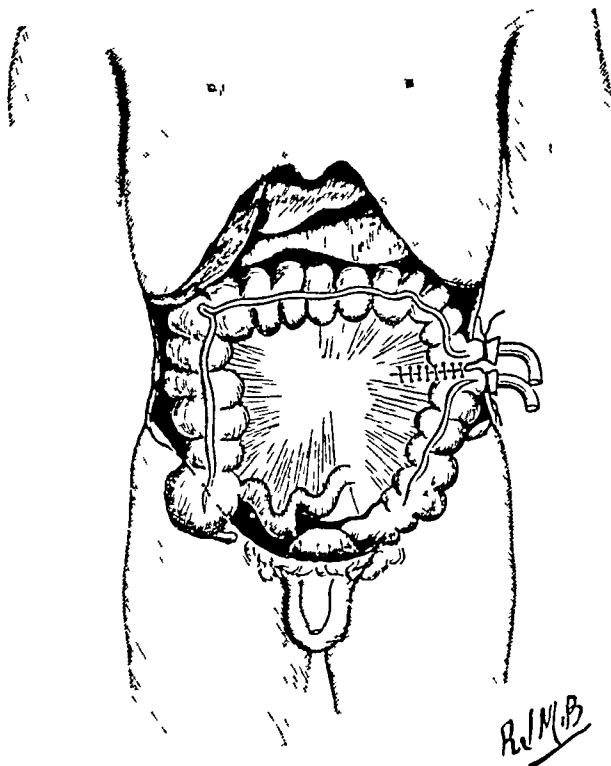


FIG 1—Reproduction of the illustration from Paul, showing the technic used (Liverpool Med Chir Jour, 1895)

1903, he²³ reported 24 operations by this method, with four deaths This mortality of 17 per cent contrasts very favorably with the 30 to 50 per cent mortality associated with immediate anastomosis of the bowel at that time

The principle of exteriorization was then adopted generally by American surgeons, who continued to practice it, under the name of the "Mikulicz procedure" for the next 20 years Both Mikulicz, in 1903, and Paul,³⁰ in his later and final article in 1912, referred to the importance of removing an adequate portion of the mesentery adjacent to the growth Paul, and Mikulicz at the time of his report, practiced immediate removal of the growth at the time of operation However, these two procedures, the immediate removal of the growth and the excision of the lymphatics and adjacent mesentery, were generally neglected by American surgeons In one large series³⁴ of cases the incidence of recurrence of carcinoma in the wound was as high as 12 per cent The mortality of the procedure, while lower than that of immediate anastomosis, was still far from satisfactory Miller,²⁴ in 1923, reported a series of 70 patients with carcinoma of the colon, treated in the Johns Hopkins Hospital from 1889 to 1919, operated upon by either

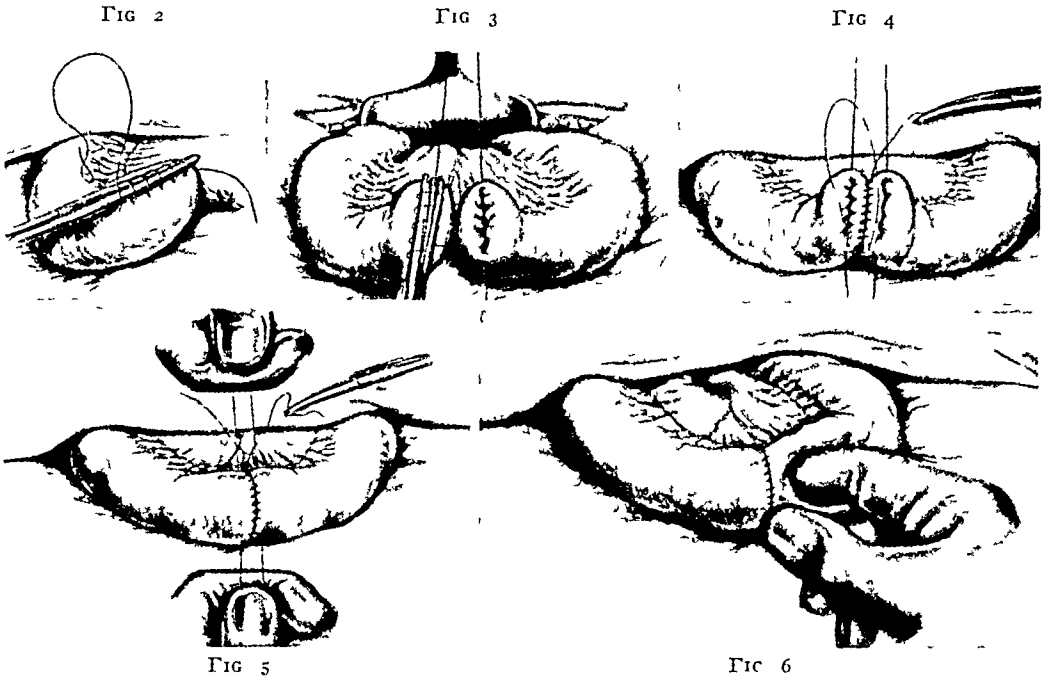
the exteriorization or open anastomosis methods. The mortality of the series was 35 per cent. Noidmann,²⁶ in 1926, reported an approximately equal mortality with resection and immediate anastomosis and the exteriorization methods. Two hundred and eighty-eight cases were operated upon by the first method with a 29 per cent mortality, while 144 patients were operated upon by the exteriorization technic with a 28 per cent mortality.

During the next decade, there was a growing dissatisfaction with this method. Sistrunk,¹⁰ in 1928, pointed out the limitations of the procedure. In 1930, Rankin¹⁴ returned to old principles in the exteriorization operation by advocating immediate removal of the tumor and wide excision of the mesentery. Clamps were left on the protruding ends of the bowel for a few days. The growing dislike of the delayed extra-abdominal anastomosis was again expressed by Cheever,⁶ in 1931 when he advised immediate anastomosis after resection of the bowel. He reported an operability of 55 per cent in patients operated upon at the Peter Bent Brigham Hospital since 1913, with the relatively low operative mortality of 18 per cent. In the decade between 1930 and 1940 Lahey,¹⁷ and Rankin³⁴ are the outstanding advocates of extra-abdominal resection and delayed anastomosis of the colon. The former¹⁶ even applies the procedure to growths in the right half of the colon, while Rankin¹⁵ prefers a primary anastomosis of the ileum and colon by an aseptic method. Both these authors have had a low operative mortality with the exteriorization operation.

Other surgeons have not been so successful. Joll,¹³ in 1938, expressed some very decided objections to the exteriorization operation, and states his preference for immediate anastomosis. Finsterlin,⁸ in 1939, shared these views. He employed immediate anastomosis whenever possible and reported an operability of 80 per cent with an operative mortality of 17 per cent. Mayo and Simpson,²¹ in the same year, reported 95 cases of exteriorization in carcinoma of the transverse colon, with an operative mortality of 20 per cent, and contrasted this with resection and primary anastomosis in 36 cases with an 11 per cent mortality.

When the older cases are included in reported series, the operative mortality remains high. Ginnel,¹² in 1939, reported a 27 per cent mortality in patients with carcinoma of the colon from 1916 to 1932. Ransom,³⁸ from Ann Arbor, in the same year, reported an operative mortality of 30 per cent in cases of carcinoma of the right side of the colon from 1925 to 1937. In the more recent series the mortality is lower. Naffziger and Bell,²⁵ in 1940, reported an 11 per cent mortality from 1930 to 1940. These last three reports included cases of open anastomosis as well as exteriorization procedures. Finally, Patterson and Webb,²⁸ in 1940, reported 70 resections of the large bowel for carcinoma, all by the exteriorization method. There were 19 deaths in 70 cases. The authors excluded seven of these deaths for various reasons. If these seven deaths are included, the operative mortality in their series is 27 per cent. Thus, it appears that the exteriorization procedure in the hands of the general surgeon still carries a high mortality.

Owing to the discomfort and the prolonged convalescence of the exteriorization method, other means of avoiding the ever constant danger of infection have been sought. Kerr¹⁵ has recently reviewed the various methods which have been proposed for anastomosing the bowel without opening its lumen. Prior to 1908, some 25 of 200 methods of intestinal anastomosis were designed to accomplish an aseptic anastomosis. Since 1908, 21 additional



FIGS 2 to 6, inclusive—Reproductions from Kerr showing the various steps in the aseptic end to end anastomosis by the basting stitch method (J A M A, 1923)

methods have been proposed. All of them are variations of the fundamental procedure of temporarily closing the cut ends of the bowel by clamps, sutures, or ligatures, uniting the bowel by suture over the temporary occluding device, and then withdrawing the clamp or suture. Only a few of the many devices or methods will be discussed here, *i e.*, those which have proved their worth in clinical practice.

Schoemaker,³⁹ in 1921, was the first to report the extensive use of an aseptic method of anastomosis of the large bowel in patients. He divided the serous and muscular coats of the bowel and then applied fine clamps to the mucosa. He cut between the clamps with a cautery and made his anastomosis with interrupted sutures, finally withdrawing the clamps. He says of the procedure: "During the whole operation, the lumen of the colon has not been opened, and we have not seen or touched the inner side of the mucosa." He performed this operation 40 times for cancer of the colon, with three deaths, an operative mortality of 8 per cent. Probably due to the stimulus of these excellent results, the decade of 1920 to 1930 was characterized by an increasing interest in the aseptic method of immediate anastomosis. In 1923, Kerr¹⁴ gave an excellent description of the clinical use of the basting-

stitch method (Figs 2 to 6, inclusive) which he and Parker²⁷ had described 15 years before. In 1924, Pingle¹¹ modified Schoemaker's method of anastomosis over clamps, by omitting the division of the seromuscular coats of the bowel. Following these descriptions of various aseptic technics, more surgeons began to apply the method clinically in carcinoma of the colon. Gibbon,¹¹ in 1932, reported 15 cases of cancer of the colon resected by the Kerr basting-stitch method, with three deaths, a mortality of 20 per cent.

During the past seven years, a number of reports have appeared contrasting the use of the aseptic method with exteriorization and open anastomosis. All of these statistical studies show a lower mortality with the aseptic technic. Wilkie,⁴¹ in 1934, reported a series of cases some of which were done by the exteriorization method and some by an aseptic technic over clamps. The mortality was lower with the latter procedure. In 1937, MacFee²⁰ reported a large series of cases from St. Luke's and the New York Hospitals, the former since 1922, and the latter since 1929. He showed a definitely lower mortality with the aseptic technic. In 1939, Stone and McLanahan⁴² reported a large series of cases operated upon by both the aseptic and open methods of anastomosis. There was a considerably lower mortality when the aseptic method was employed. In the same year, Allen¹ discussed a large series of cases of carcinoma of the colon occurring at the Massachusetts General Hospital. The operability was 58 per cent, and the operative mortality 24 per cent. He expressed a strong preference for the aseptic Parker-Kerr anastomosis preceded by colostomy or cecostomy, and in the sigmoid colon, he reported an operative mortality of 14 per cent by aseptic methods and 23 and 21 per cent by the open and exteriorization methods, respectively. In 1939, Wilkie⁴³ contrasted the exteriorization and aseptic technics in a larger series of his own patients and again found a lower mortality with the latter procedure.

Aside from contamination occurring at the time of operation which the aseptic methods attempt to avoid, there is always the danger of late peritonitis five or ten days after the operation from necrosis or leakage at the suture line. This danger is perhaps easily as great as that of immediate contamination during the operation, and has been responsible for the continuation of the use of exteriorization in the presence of adequate aseptic methods of anastomosis. Because of this constantly recurring danger, lateral anastomosis was early proposed as a safer procedure than end-to-end union of the large bowel, in the belief that there would be fewer instances of leakage from the suture line. The anastomosis is made along the antimesenteric border of the bowel without interrupting the blood supply to the wall of the colon. With the end-to-end anastomosis however, if the bowel is divided at right angles to its long axis, there is danger of necrosis along the antimesenteric portion of the suture line because of the vertical direction of the small terminal arteries supplying the wall of the intestine. These arteries may be crushed by the clamp or included in a ligature, thus interfering with the blood supply of the antimesenteric border of the bowel.

In 1917, Lockhart-Mummery¹⁸ published a classic report on the advantage of end-to-end, as opposed to side-to-side, anastomosis. He pointed out the dangers of leakage from bowel contents being driven by peristaltic action against closed ends of the bowel with the lateral anastomosis. He believed that the failures with end-to-end anastomosis in the past were due to improper attention to the terminal blood vessels of the colon which pass around the bowel wall at right angles to its long axis. He, consequently, advised cutting the bowel at an angle, so that a greater portion of the antimesenteric border was removed, thus insuring an adequate blood supply to the cut margins of the bowel. Kerr¹⁴ in 1923, again urged the advantages of end-to-end anastomosis. Meillère,²² in 1927, published an excellent account of the blood supply of the wall of the colon, and its surgical applications. He injected the vessels supplying the normal colon and studied the relation of the terminal arteries to the appendices epiploicae. The injections were then repeated after various ligations of the arteries. He confirmed Lockhart-Mummery's opinion that it was best to divide the colon obliquely, removing more of the antimesenteric than of the mesenteric border of the bowel, thus insuring an adequate blood supply to the cut ends of the bowel. He believed that it was safe to remove the fat for a short distance from the cut ends of the colon before suturing, but recommended exercising great care in removing the appendices epiploicae, as the straight terminal arteries supplying the wall of the colon run in the base of these appendices. Stewart and Rankin,⁴¹ in 1933, also published an excellent study of the blood supply to the walls of the colon. A correct appreciation of the blood supply to the colon should obviate the danger of necrosis at the suture line in end-to-end anastomosis.

It has not been borne out in reported series of cases, that the mortality of the side-to-side anastomosis is lower. Miller,²⁴ in 1923, reviewing cases of carcinoma of the colon at Johns Hopkins Hospital, found a higher mortality with lateral, as opposed to end-to-end anastomosis. Raiford,³² in 1933, advised lateral anastomosis in resection of the transverse colon. However, two years later, in reviewing a large series of cases of cancer of the colon, he³³ found the operative mortality almost three times higher with lateral anastomosis as compared with end-to-end union.

The recent wide adoption of chemotherapy for the control and treatment of infection will undoubtedly lower the mortality of resection of the colon for cancer. Garlock and Seley¹⁰ were the first to report the use of sulfanilamide in resections of the colon. In a series of cases, they made cultures from the serous surface of the colon, from the muscular walls and from the surface of malignant growths. They found the predominating organism to be the hemolytic streptococcus. On the basis of this study, they administered sulfanilamide orally prior to and following operations on the colon. In this group of patients, at the time of operation, the same type of cultures were repeated and hemolytic streptococci were found to be absent in all instances. They reported nine resections of the colon for carcinoma, with one death.

This fatality was not due to peritonitis. In the following year, Lockwood and Ravdin¹⁰ reported using sulfanilamide preceding and following 11 resections of the colon for carcinoma. There was one death from coronary thrombosis. Frier,¹¹ in December, 1940, was the first to report on the use of sulfamylguanidine in colonic surgery. The drug was administered for about one week preceding operation in a series of patients which included some very difficult resections and anastomoses of the large bowel. There were no fatalities and no instances of peritonitis, in spite of gross contamination and soiling in a number of cases.

The present report is based upon a series of 120 patients with carcinoma of the colon proximal to the rectosigmoid. It comprises all patients with carcinoma of the colon admitted to the Pennsylvania and the Bryn Mawr Hospitals from 1928 to 1941. Nine of these patients refused operation, or died shortly after admission without being operated upon. In 52 patients, the growth was found to be inoperable but 59 of the remaining 111 patients underwent radical resection of the colon, an operability of 53 per cent. There were 15 deaths in the hospital following operation, an operative mortality of 25 per cent. The operations were performed by 20 different surgeons (Table I). Five surgeons operated upon 80 of the patients, the remaining 31 patients were operated upon by 15 surgeons. As can be seen in Table I, the more experienced surgeons had operability rates varying between 50 to 83 per cent. The other 15 surgeons had the very low operability rate of 29 per cent. The operative mortality of the five experienced surgeons varied between zero and 37 per cent, the higher mortalities being associated, in general, with higher rates of operability.

TABLE I
RECORD OF INDIVIDUAL SURGEONS

Surgeon	Number of Patients Operated Upon	Number of Patients from Whom Tumor Was Removed	Operability Per Cent	Deaths in Hospital Where Tumor Was Removed	Hospital Mortality Where Tumor Was Removed Per Cent
A	22	15	68	5	33
B	20	10	50	2	20
C	14	7	50	0	0
D	12	10	83	3	30
E	12	8	67	3	37
15 surgeons	31	9	29	2	22
Totals 20 surgeons 111		59	53	15	25

When the resections are grouped according to the type of operation performed, it can be seen that the aseptic anastomosis has the lowest operative mortality, 13 per cent (Table II). The aseptic anastomoses were performed by the Kerr basting-stitch method in all these patients. Exteriorization is next in order with 29 per cent, whereas the open anastomoses had an operative mortality of 38 per cent. Conversely, the number of patients alive and

without evidence of metastasis is higher in the group with aseptic anastomosis, and smallest in the group with the open anastomosis

All five of the more experienced surgeons employed more than one type of operation upon their patients. The results obtained by these five surgeons can be seen in Table III. The operative mortality again was lowest with

TABLE II
CASES IN WHICH TUMOR WAS REMOVED

Type of Operation	Number of Patients	Deaths in Hospital		Living Without Metastasis	
		Number	Per Cent	Number	Per Cent
Aseptic anastomosis	24	3	13	9	38
Exteriorization	14	4	29	4	29
Open anastomosis	21	8	38	4	19
Totals	59	15	25	17	29

TABLE III
MORTALITY WITH DIFFERENT TECHNIQUES OF SURGEONS A B C D AND E

	Aseptic Anastomosis	Exteriorization	Open Anastomosis
Patients	20	11	19
Deaths in hospital	3	3	7
Mortality per cent	15	27	37

the aseptic anastomosis, 15 per cent, next with exteriorization, 27 per cent, and very high with open anastomosis, 37 per cent. The wound complications (Table IV) were more frequent with open anastomosis than with the other

TABLE IV
WOUND COMPLICATIONS

Type of Operation	Wound Infections		Abscess or Local Peritonitis		General Peritonitis		Evisceration		No Complication	
	No	Per Cent	No	Per Cent	No	Per Cent	No	Per Cent	No	Per Cent
Aseptic anastomosis	5	21%	2	8%	2	8%	1	4%	14	58%
Exteriorization	2	14%	0	0%	3	21%	0	0%	9	64%
Open anastomosis	5	24%	4	19%	3	14%	0	0%	9	43%

two types, in which the incidence was approximately the same. General peritonitis occurred more frequently following the open anastomosis and exteriorization than it did with the aseptic methods.

In Table V, the type of operation performed in different regions of the colon is shown. In the right colon, ten resections were performed by the aseptic technique with no deaths, while with the open anastomosis there were three deaths in ten cases. There were only two resections of the transverse colon, and both were without mortality. There was little difference in the mortality of the three methods in the splenic flexure and descending colon. In the sigmoid colon, there was little difference between the aseptic and exteriorization methods, whereas the operative mortality with open anastomosis was 80 per cent.

The question as to whether cecostomy or colostomy should be employed

ASEPTIC ANASTOMOSIS

TABLE V
TYPE OF OPERATION

Location of Lesion	Aseptic Anastomosis			Exteriorization			Open Anastomosis			Totals		
	Cases	Deaths	Mort Per Cent	Cases	Deaths	Mort Per Cent	Cases	Deaths	Mort Per Cent	Cases	Deaths	Mort Per Cent
Cecum, ascending colon, hepatic flexure	10	0	0%	1	0	0%	10	3	30%	21	3	14%
Transverse colon	1	0	0%	0	0	0%	1	0	0%	2	0	0%
Splenic flexure and descending colon	4	1	25%	3	1	33%	5	1	20%	12	3	25%
Sigmoid colon	9	2	22%	10	3	30%	5	4	80%	24	9	38%

preceding a direct attack on the tumor has been discussed for many years. It is generally agreed, at present, that if any degree of obstruction exists, a preliminary decompression should be undertaken. It is also agreed that a certain number of cases do not require such a preliminary operation. However, it is probably always safer, even in the patients without obstruction, to perform a cecostomy at the time of operation, when a primary anastomosis of the left colon is performed.³⁷ Table VI contrasts the mortality in the cases without decompression, with the mortality in cases in which the bowel was decompressed, either previously, or at the time that the tumor was removed. With the aseptic technic there was no difference in the operative mortality, although twice as many cases were performed without any decompression. With exteriorization and open anastomosis, the mortality was much higher in the cases without decompression of the bowel.

TABLE VI
CECOSTOMY AND COLOSTOMY

Type of Operation	Decompression of the Bowel Before or at Time of Operation			No Decompression of the Bowel		
	Number of Patients	Deaths in Hospital	Operative Mortality Per Cent	Number of Patients	Deaths in Hospital	Operative Mortality Per Cent
Aseptic anastomosis	8	1	13%	16	2	13%
Exteriorization	9	2	22%	5	2	40%
Open anastomosis	12	3	25%	9	5	56%
Totals	29	6	21%	30	9	30%

Appended are brief histories of the 15 patients who died following operation.

ABBREVIATED CASE REPORTS

Case 1—Female, age 50, with carcinoma of descending colon. August 1, 1928, resection, with open end-to-end anastomosis. Had febrile postoperative course. Numerous stools per rectum on third, fourth, and fifth postoperative days. On sixth postoperative day, pain in upper left quadrant of abdomen accompanied by tenderness and generalized abdominal distention. Pulse rate and temperature both rose. Signs of circulatory collapse developed seven hours later, and patient died eight hours after onset of pain, presumably from peritonitis and gross leakage at the suture line. No postmortem.

Case 2—Male, age 35, with carcinoma of the sigmoid September 19, 1928, the growth in the sigmoid, together with the left half of the colon was resected, and an open anastomosis was performed between the midsigmoid and the midtransverse colons. The proximal bowel was distended. No cecostomy was made. The temperature was elevated from the first postoperative day. He died six days after operation with signs and symptoms of peritonitis. No postmortem.

Case 3—Male, age 75, with carcinoma of the sigmoid October 22, 1928, entire left colon resected because of involvement of the transverse colon in the malignancy. Open anastomosis performed between the transverse and sigmoid colons, with some contamination. A colostomy with mushroom catheter was made just proximal to the site of the anastomosis. The patient developed pyelonephritis and uremia. He had to be catheterized throughout the postoperative course. Death occurred on the fourteenth postoperative day, presumably from renal failure. There was no evidence of peritonitis at any time. No postmortem.

Case 4—Male, age 61, with carcinoma of the sigmoid November 16, 1928, sigmoid resected and end-to-end aseptic anastomosis made by Kerr basting-stitch method. Two continuous sutures of catgut were used to make the anastomosis. There was no obstruction, and no cecostomy was performed. There were no bowel movements following operation. On the sixth postoperative day, there was evidence of peritonitis. The patient was operated upon, generalized peritonitis found, and the abdomen drained. The patient died on the seventh postoperative day.

Case 5—Male, age 58, with carcinoma of the sigmoid November 5, 1930, the sigmoid was resected, and an open anastomosis performed. Death occurred two days later with signs and symptoms of generalized peritonitis. No postmortem.

Case 6—Female, age 55, with carcinoma of the descending colon November 13, 1930, a loop-colostomy of the transverse colon was made because of obstruction. No spur was formed. The colostomy was not opened for 11 days. Two months later, an open side-to-side ileosigmoidostomy was performed. Two months later still, the descending colon, with the growth was removed and the ends of the colon inverted. Death occurred one month later. Postmortem examination revealed that the blind end of the colon at the splenic flexure had opened. There was a sinus tract extending down to the left lower quadrant of the abdomen, with extensive ramifications in the abdominal wall.

Case 7—Female, age 66, with carcinoma of the descending colon September 8, 1931, the first stage of an exteriorization operation was performed. The growth was withdrawn from the abdomen and the limbs of the colon were sutured together and to the parietal peritoneum. Three days later the bowel containing the growth was removed. Death occurred on the same day with signs and symptoms of peritonitis. There had been a gradually increasing temperature and pulse rate and marked distention since initial operation. No postmortem.

Case 8—Female, age 80, with carcinoma of the descending colon April 26, 1933, cecostomy was performed because of an obstruction. Twenty-two days later the descending colon with the growth was resected by the Kerr basting-stitch method. Some contamination occurred when the ends of the colon were inverted by the basting-stitch. Death occurred four days later with signs and symptoms of peritonitis. No postmortem.

Case 9—Female, age 53, with carcinoma of the ascending colon August 22, 1934, the right half of the colon was resected and an open side-to-side anastomosis made between the ileum and the transverse colon. The patient died on the seventh postoperative day, with signs and symptoms of generalized peritonitis. No postmortem.

Case 10—Male, age 79, with carcinoma of the sigmoid May 29, 1935, the growth was exteriorized. The patient died three days later, with signs and symptoms of generalized peritonitis. No postmortem.

Case 11—Male, age 63, with carcinoma of the sigmoid December 18, 1935, the growth was resected and a primary anastomosis performed by the Kerr basting-stitch method. Cecostomy was performed at the time of operation. The patient had no bowel

movements by rectum for 11 days following the operation. After this he had normal stools. Twenty-one days after operation the patient died, with signs and symptoms of bronchopneumonia, probably secondary to congestive failure, as there were râles throughout his lungs for ten days before death. No postmortem.

Case 12—Female, age 54, with carcinoma of the hepatic flexure. September 26, 1936, an open side-to-side ileosigmoidostomy was performed because of obstruction. Twenty-four days later the right colon was resected, and the blind ends of the transverse colon and the terminal ileum inverted. Five days after operation the patient died, with signs and symptoms of general peritonitis. At autopsy, the peritonitis was found to be due to leakage from the end of the blind stump of the transverse colon.

Case 13—Male, age 69, with carcinoma of the sigmoid and partial obstruction for eight days. July 7, 1939, the growth was withdrawn from the abdomen through a right lower rectus sheath incision. The limbs of the bowel were sutured together and to the parietal peritoneum. The mesentery was not excised. Three days after operation, the proximal loop of the colon was opened and a catheter inserted. Death occurred the following day, four days after operation, following a gradual rise in temperature and pulse rate. Death was probably due to peritonitis, the infection originating from the sutures introduced into the distended proximal loop of bowel. No postmortem.

Case 14—Male, age 53, with carcinoma of the sigmoid. November 29, 1937, the growth was exteriorized. He developed a wound infection and died on the twelfth post-operative day.

Case 15—Male, age 69, with carcinoma of the ascending colon. May 4, 1939, the right half of the colon was resected and an open anastomosis made between the terminal ileum and the transverse colon. There was some contamination of the operative field. The patient developed a wound infection and a localized peritonitis, and later a fistula of the ileum. He ran a progressive downhill course and died ten weeks after operation. No postmortem.

In analyzing these deaths, it is apparent that the mortality is chiefly due to infection. Of the 15 deaths in this series, ten were due to generalized peritonitis, three to wound infections and localized peritonitis, and two to causes probably unrelated to the operation. Of the ten deaths from peritonitis, five followed resection with open anastomosis of the colon. Two of these were of the right side of the colon and three of the left. Generalized peritonitis occurred following the first stage of an exteriorization procedure in three patients. Two of the growths were in the sigmoid and one in the descending colon. Finally, two of the ten deaths due to peritonitis followed an aseptic anastomosis. In one case, a cecostomy to protect the suture line was not performed, in the other case, contamination occurred during the operation from an error in the aseptic technic. There were three deaths from wound infection and localized peritonitis. All three lesions were in the left half of the colon, two following open anastomosis of the bowel and one following the first stage of an exteriorization procedure.

Four reports have appeared contrasting the operative mortality of aseptic anastomosis with the mortality of exteriorization or open anastomosis. These four reports have been summarized in Table VII. Two hundred and forty-six aseptic resections of the colon were performed with an operative mortality of 14 per cent. One hundred and twenty-four exteriorization operations were performed, with a mortality of 27 per cent. Seventy-two open anas-

TABLE VII

OPERATIVE MORTALITY IN RESECTION OF THE COLON FOR CARCINOMA BY AUTHORS USING DIFFERENT METHODS

Author	Number of Patients	Deaths in Hospital	Operative Mortality Per Cent	Type of Operation
MacFee	56	9	16%	Aseptic anastomosis
Wilkie	95	15	16%	
Stone and McLanahan	71	8	11%	
Gibbon and Hodge	24	3	13%	
Totals	246	35	14%	
MacFee	68	19	28%	Exteriorization
Wilkie	42	9	21%	
Gibbon and Hodge	14	5	36%	
Totals	124	33	27%	
MacFee	32	6	19%	Open anastomosis
Stone and McLanahan	19	5	26%	
Gibbon and Hodge	21	8	38%	
Totals	72	20	28%	

tomoses were performed, with a mortality of 28 per cent. Thus, in this group of patients the operative mortality with exteriorization or open anastomosis is approximately double the mortality associated with aseptic anastomosis.

The surgical therapy of tumors of the colon, proximal to the rectum and rectosigmoid, involves resection of the bowel with the contained tumor and the reestablishment of the continuity of the gastro-intestinal tract. This surgical procedure is fraught with great danger of infection because the lumen of the colon contains more virulent bacteria than are found in any other portions of the body. The chief problem in the surgical therapy of cancer of the colon is now, and always has been, the avoidance of peritonitis. The means of avoiding such infection may be briefly summarized under four heads:

(1) No type of major operative procedure to remove the growth should be performed in the presence of any degree of obstruction of the colon. The obstruction should always be relieved first by drainage of the colon through a cecostomy⁴³ or colostomy. When the latter procedure is employed, it should always be performed at a considerable distance proximal to the growth, *i. e.*, in the right half of the transverse colon, in order not to interfere with subsequent operative manipulations involved in the removal of the tumor. In obstruction of the right half of the colon, which cannot be relieved by non-operative means, the fecal current should be diverted by an ileotransverse colostomy.

(2) Contamination of the peritoneum and of the abdominal wound should be avoided at the time of the operative attack on the tumor. This can be done either by exteriorization of the growth with its removal after closing the abdominal incision, or by performing the anastomosis by some form of aseptic technic, in which the lumen of the colon is not opened or entered during the performance of the anastomosis. It is more difficult, and time-consuming, to avoid contamination in an open anastomosis than when an aseptic method is used.

(3) Late peritonitis is almost always the result of leakage from the suture line, or necrosis of the bowel wall where primary anastomosis has been performed. Such a catastrophe is often due to interference with the blood supply to the wall of the colon at the site of the anastomosis, and can be prevented by proper knowledge and technic. In addition, the performance of a cecostomy at the time of the primary anastomosis where the growth involves the left half of the colon will help to avoid distention of the bowel above the anastomosis,³⁷ which is a factor in producing leakage and peritonitis. The late peritonitis which follows exteriorization procedures is probably due either to infection arising from sutures entering the bowel lumen when the spur is formed, or to necrosis of the bowel as it passes through the abdominal wall from interference with its blood supply. Both these complications can be avoided by suitable technic.

(4) The sulfonamides are of undoubted value in colonic surgery. Sulfanilamide should be used orally and locally at the time of operation, until other compounds have been shown to be superior in controlling accidental contamination.

SUMMARY

One hundred and twenty cases of carcinoma of the colon, proximal to the rectosigmoid, have been reviewed. These cases comprise all the patients admitted to the Pennsylvania and the Bryn Mawr Hospitals for this condition from 1928 to 1941. One hundred and eleven of these patients were operated upon, and in 59 the tumor was removed, an operability rate of 53 per cent. The gross mortality of the whole series of patients in which the tumor was removed was 25 per cent.

The purpose of this study is to determine the operative mortality of the three main types of operative procedures: Aseptic immediate anastomosis, extra-abdominal resection, with delayed anastomosis, and immediate anastomosis of the opened bowel. Twenty-four patients were operated upon by the aseptic technic, three of these died in the hospital, giving an operative mortality of 13 per cent. Fourteen patients were operated upon by exteriorization methods, with four deaths in the hospital, an operative mortality of 29 per cent. In 21 patients, an open anastomosis of the bowel was performed, with eight deaths in the hospital, an operative mortality of 38 per cent.

This series of cases is too small to have statistical significance. However, when these statistics are combined with those reported by MacFee, Wilkie, and Stone and McLanahan, the combined percentages are probably of real significance. Two hundred and forty-six patients were operated upon by the aseptic technic, with 35 deaths, an operative mortality of 14 per cent. One hundred and twenty-four patients were operated upon by exteriorization methods, with 33 deaths, an operative mortality of 27 per cent. Finally, 72 patients underwent an open anastomosis of the colon. Twenty of these patients died, an operative mortality of 28 per cent.

These combined statistics appear to indicate that in the hands of the general surgeon aseptic, immediate anastomosis is the operation to be preferred

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DISCUSSION—WILLIAM F MACFEE, M D (New York, N Y) The surgical removal of carcinoma of the colon, as Doctors Gibbon and Hodge have said, was seldom undertaken in the days of antiseptic surgery As a matter of fact, celiotomy was not often undertaken for any purpose

With the establishment of asepsis, abdominal surgery received a great impetus, and there were some who had the hardihood to attempt the removal of cancer of the colon Apparently, the number was few because, according to Rankin, only ten resections were on record in 1880, seven of these had failed, a mortality of 70 per cent Rankin states that the number of resections had increased to 48 by 1890, and the mortality had decreased to 45 per cent Heineke described an exteriorization operation in 1884, but it is probable that all of the resections reported, up to 1890, were done by the open method within the abdomen

The operation for which Bloch, Paul, and Mikulicz share credit, brought about a substantial reduction in the operative mortality and the exteriorization procedure was widely accepted, but like all other operations it was not without faults, and its universal application was soon questioned

Reichel, in 1911, contended that the results of primary resection carried out under proper conditions compared favorably with the results of resection preceded by exteriori-

zation, and offered statistical proof of his contention. His criteria for primary resection were

(1) That the general condition of the patient must be such that a somewhat lengthy operation is permitted

(2) The intestine proximal to the tumor must not harbor any considerable accumulation of fecal material

(3) The intestine must be viable and free of circulatory disturbances

(4) It must be possible to suture the ends of the intestine together without tension

He also admonished care in placing the sutures, accuracy of approximation, and emphasized exactitude rather than speed of operation. These rules are as sound to-day as when first formulated.

During the 30 years that have passed since Reichel proposed these criteria of safety, the development of relatively aseptic methods of anastomosis has further diminished the risks of end-to-end suture. Doctors Gibbon and Hodge, and others, have shown that, with suitable precautions, aseptic, immediate anastomosis has a lower mortality rate than methods which are commonly presumed to be more conservative. This appears to be true even when the operating is distributed among a considerable number of the Surgical Staff of a General Hospital. It is also a matter of significance that the largest number of patients who were well and free of recurrence in Doctors Gibbon and Hodge's series was in the group with aseptic anastomosis.

Considerably less than one-half of the patients who present themselves to an hospital, with carcinoma of the colon, subsequently leave with any chance of surviving the disease. Some are inoperable from the outset, some die following operation, some survive the operation but harbor metastatic tumors, which cannot be eradicated. Since the inoperable cases and those having remote metastases cannot be permanently benefited, it becomes all the more important not to lose, through operative mortality, those who have a reasonable chance of cure. The results of Doctors Gibbon and Hodge's study of a representative series of cases appears to indicate that this objective will be promoted by the further development and more widespread use of aseptic anastomosis.

DR WILLIAM B PARSONS (New York, N. Y.) I am very glad that Doctor Gibbon has brought forward this very interesting paper and has emphasized some of the points in safe large bowel surgery.

I would like to speak for just a moment on the question of the right colon and not so much about the left colon. The niceness of the anastomosis, the niceness of the technic, and the prevention of immediate contamination is, of course, important. Unquestionably, the big danger is subsequent leakage, the main point in that is the question of decompression. Both Doctors Gibbon and MacFee spoke about the need of decompression.

At the next meeting of the American Medical Association, Doctor Leigh, of the Presbyterian Hospital, is going to report on the use of the Miller-Abbott tube. In the past two years that has been a method of real importance in reducing the operative mortality. There are several points about the employment of the tube that Dr. Leigh will emphasize in his report, one of them being that it must be introduced prior to operation, and the tube must be in the small bowel before the operation is begun. Among other points, he will report that during the past two years, at the Presbyterian Hospital in New York, with a number of men performing the surgery, the mortality without the use of the tube was 22 per cent, but with its use it was 67 per cent.

DR RICHARD B CATTELL (Boston, Mass.) This has been a very interesting discussion to me, since from our experience at the Lahey Clinic we carry out resections of the colon by means of the exteriorization principle, and since the paper of Doctors Gibbon and Hodge contrasts the two methods, it seems reasonable to present our experience in dealing with the exteriorization procedure.

Since 1929, but one case has had a primary resection, with aseptic anastomosis. The rest have all been operated upon in two stages, and 90 per cent of all resections by a modified Mikulicz plan. During this time, approximately 275 patients have had resections by employing the exteriorization procedure, with a mortality of 13 per cent. Of those followed over five years, 53.6 per cent of those resected have had no evidence of recurrence.

The slide that Dr. Gibbon showed of operability is a thing that interests us most. It was approximately 53 per cent in his group of cases. We believe that the employment of the exteriorization principle will enable us to markedly raise the operability in these

cases One will not venture to perform an intraperitoneal anastomosis with a dilated and distended bowel, because of the possibility of postoperative infection from leakage from the suture line, and it is in these cases that the exteriorization principle can be applied with reasonable safety, at least as borne out by our experience In other words, we can offer relief to a larger number of the unfavorable cases by the utilization of this method and furthermore, we believe it is a safe method for all resections of the colon

DR HARRY H KERR (Washington D C) After Doctor Cattell's talk on exteriorization, I might review some cases that were recently gathered for another presentation, where only resection was considered, with immediate mortality, without comparing the exteriorization operation, with resection

In a study of all cases of intestinal resection performance at the Garfield Memorial Hospital in Washington, to determine the value of the aseptic technic over the open method, 107 operative records were reviewed Sixty-eight resections had been performed by the open method and 39 by the aseptic basting-stitch technic The list includes all resections done in that time, and of course contains many desperate cases of strangulation, intussusception, etc Garfield is not a closed hospital and is open to all the good surgeons of the city Therefore the study records the work of many surgeons

In the cases resected by the open method, there was an immediate mortality of 35 per cent In the cases resected by the basting-stitch technic, the immediate mortality was 15 per cent

In a review of my own private cases of intestinal resection, all done with the basting-stitch technic, I have records of 40 cases, with a hospital mortality of 12.5 per cent That, corrected for immediate mortality by autopsy on two of the cases that died (one of uremia and another of pneumonia) would reduce the mortality to about 7 per cent The list includes nine cases of resection for Hirschsprung's disease, with no deaths

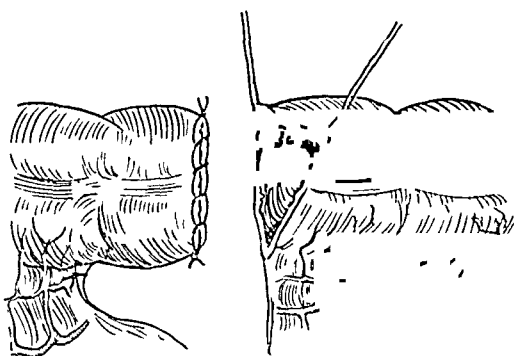
I do not think there is any question that the profession has accepted the idea that direct end-to-end anastomosis is the most physiologic and the preferred operation for resection, and I do not doubt that the Miller-Abbott tube, and possibly the sulfamidamide groups, will further reduce our mortality

DR WARFIELD M FIROR (Baltimore) Rather than quote statistics, I think it may be pertinent if we ask ourselves a question What is the cause of death in those cases in which the Mikulicz procedure is employed? It seems to be obvious that there are two main causes First the spread of infection when closure is attempted, and, second, the fact that the patient is hospitalized for a long period of time

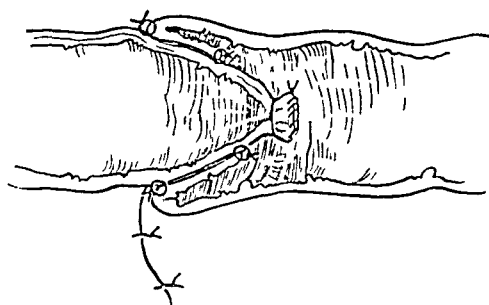
It is conceivable that the advantages of the Mikulicz procedure may be utilized and also those of an end-to-end anastomosis, if some sulfonamide compound can be found which can be used after the first stage of the Mikulicz procedure We have had six cases in which sulfanilylguanidine has been so employed, and in every instance with an intact mucuous membrane following the removal of the growth, the bacterial count has fallen to an insignificant number We have felt justified, therefore, in performing an end-to-end anastomosis and replacing the intestine in the peritoneal cavity, thereby shortening the period that is required for closing the bowel in the ordinary Mikulicz operation

DR LEO EROSSER (San Francisco) There is a difference between carcinomata of the lower bowel, with obstructive symptoms and those without It may be best to treat carcinomata with obstruction by resection and exteriorization of the afferent loop, and those without obstruction by resection and immediate anastomosis An invagination operation which is a compromise between Kerr's aseptic anastomosis and an open operation, is simple and satisfactory both for immediate anastomosis and closure of a colostomy Resection is performed aseptically, between clamps The upper segment is closed by a fine catgut suture, its mesentery is freed for about one inch or one inch and one-quarter back from the site of resection, the triangle formed by the two leaves of the mesentery and the bowel wall is closed by a fine catgut suture The closed upper segment is then invaginated into the lower segment and the two are united by one or two layers of sutures through their serous and muscular coats The upper segment thus hangs into the lower one like a cervix into the vaginal vault Recently, I have closed the upper segment by a fine catgut suture that approximated the two opposing mucous coats instead

of putting in a basting-stitch approximating the serosa. This mucous stitch holds for a few days only, the basting-stitch through the serous coat has kept the bowel closed so long that I often feared it never would open. Although the lower segment is opened momentarily while the upper one is invaginated into it, contamination is minimal, for the upper segment is kept aseptically sealed throughout.



(a) Afferent limb closed ready for invagination



(b) Cross section of completed anastomosis

the collected series here, of 246 cases, gave approximately the same mortality with the aseptic method. Thus the exteriorization method in expert hands certainly does give an adequately low mortality.

DR JOHN H GIBBON, JR (Philadelphia, closing). In regard to a point which was raised by Doctors Firor and Cattell, we have the conviction that it is a mistake to perform any operative procedure upon the tumor in the case of obstruction. We think that the ideal preliminary procedure in obstruction of the left colon is a transverse colostomy or cecostomy. In lesions in the right colon, a preliminary decompression is rarely necessary. If a decompression is done and the bowel cleaned, all cases, then, are readily susceptible to primary anastomosis. In our series we found that when exteriorization was done in the face of obstruction there was often a great deal of trouble.

I was interested to see that Doctor Cattell's mortality at the Lahey Clinic was 13 per cent with the exteriorization method, and

CHRONIC ULCERATIVE COLITIS[†]

A SUMMARY OF EVIDENCE IMPLICATING *BACTERIUM NECROPHORUM*
AS AN ETIOLOGIC AGENT

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IT IS THE PURPOSE of the present communication to present a summary of a study on the problem of chronic ulcerative colitis carried on as a joint enterprise in the Departments of Surgery, Bacteriology, and Medicine of the University of Chicago during the past eight years. Most of the data presented in previous reports³ has been confirmed in our further experience and considerably amplified. As a result of this work we are persuaded that *Bacterium necrophorum*, together with factors, some of which are at present unknown, plays an etiologic rôle in the disease.

It has long been recognized that the part played by bacterial infection in chronic ulcerative colitis, as in other enteric infections, has been difficult of solution to a large extent because of the extraordinary variety and abundance of the normal intestinal flora. The nature of the bacterial species in the various levels of the normal gastro-intestinal tract and their relative abundance has been found to depend among other things on the type of organisms ingested with the food, the presence of foci of infection in the nose and mouth, the acidity of the gastric secretion, the rate of passage of the fecal current, and perhaps of greatest importance on the character of the diet. It is small wonder, then, that cultures taken from the colon discharges or from lesions, seen with the proctoscope, in patients with chronic ulcerative colitis have yielded a wide variety of organisms and little agreement among investigators.

A number of years ago, in a study of the problem of acute intestinal obstruction, one of us together with Moorhead and Buicky¹ made the observation that segments of the intestine isolated from continuity with the alimentary tract but retaining their normal blood supply become sterile after the passage of time. Thus, a segment of jejunum or ileum, isolated as in Figure 1, and washed with sterile water to remove solid material, becomes sterile in a few weeks if dropped back into the peritoneal cavity. Dack² has similarly observed that such segments drained to the outside as in the Thiry-Villa fistula also become sterile if undisturbed by the trauma of irrigation or injection. The factors involved in this self-sterilization seem to be

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chiefly mechanical and consist in the protective action of the intestinal mucus, which entangles the organisms, and peristalsis which steadily propels them along the tube. It occurred to us then that a study of the bacteria in the colon of patients with chronic ulcerative colitis ought to be more significant when the diseased colon is isolated from the fecal stream and the processes of self-sterilization are operative, in which case the organisms that might be found to persist ought to be of greater significance than the birds of passage

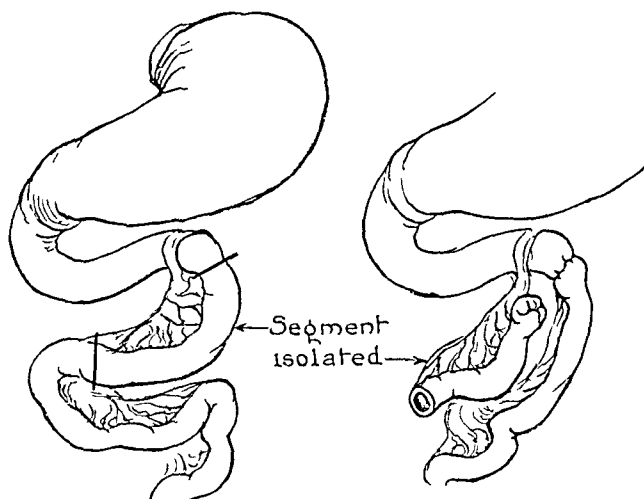


FIG 1—Diagram illustrating an isolated segment of jejunum sterilized by prolonged drainage into the peritoneal cavity

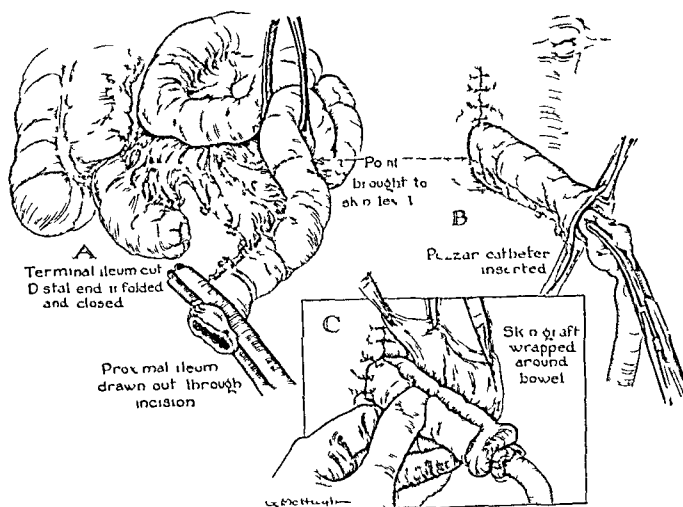


FIG 2—Diagram illustrating a method for end ileostomy

It is not our purpose to discuss the merits of ileostomy in the treatment of chronic ulcerative colitis. It is our conviction that the procedure is definitely beneficial when so performed that irritation and digestion of the abdominal wall does not occur. The method that we have employed will be presented in detail elsewhere and a short description will suffice here (Fig 2). The abdomen is opened through a short, low right rectus incision. The ileum

is transected about four inches from the cecum and the distal end closed. The mesenteric vessels supplying the lower six inches of the proximal end of ileum are divided about an inch from the point where they enter the intestinal wall, in order to preserve the distal arcade and thus prevent necrosis of the portion of ileum that is to be exteriorized. The ileum is then brought out six inches beyond the skin surface and the wound closed loosely, with the mesenteric



FIG. 3.—Photograph showing appearance of the skin covered ileostomy three months after the operation. Note the absence of excoriation of the surrounding skin.

border sutured at the lower end of the incision so that the exteriorized ileum will arch downward. A small Pezzar catheter is then tied into the lumen of the bowel to drain off the intestinal content. A rectangular segment of skin, four by eight inches in size and six one-thousandths of an inch thick is then cut from the neighboring abdominal wall with a Padgett dermatome and wrapped carefully around the exteriorized portion of ileum suturing it only

to the skin of the abdominal wall which surrounds the fistula. A gauze pressure-dressing completes the operation. The Pezzar catheter usually remains intact for six days when the dressing may be removed. A complete take of the graft has occurred in the four cases where we have employed this



FIG 4—Photomicrograph showing a pure culture of *Bacterium necrophorum* from an anaerobic blood agar plate ($\times 2700$)



FIG 5—Photomicrograph showing the characteristic morphology of *Bacterium necrophorum*, pleomorphism and filamentous forms ($\times 2700$)

procedure. The resulting ileostomy looks somewhat like a penis and may be easily fitted with an ileostomy bag. The absence of excoriation of the skin is illustrated in the photograph in Figure 3.

At the present time, we have data on the bacteriology of the colon in 12 patients with chronic ulcerative colitis in whom the fecal current has been diverted by end-ileostomy. The symptomatology, roentgenographic and proctoscopic observations were in each case characteristic of the severe form of the disease. All had been treated in the Medical Service for varying periods of time, and were finally referred for surgical treatment because of

progressive cachexia anemia and persistence of local symptoms. Cultures from saline washings of the colon were secured before operation at weekly intervals for the first two or three months afterward and at irregular intervals during the following years. A strikingly similar result was observed in all. With the diversion of the fecal current aerobic organisms began to diminish



FIG. 6—Anaerobic blood agar plate from a swab culture secured at procedure examination from an area of colon acutely ulcerated in a patient with chronic ulcerative colitis. The colonies are dark, irregular, and numerous. They are *Bacterium dysenteriae*.



FIG. 7—Anaerobic plate showing a culture from the same patient as in Figure 6 but taken from an area of mucosa not acutely involved. No colonies of *Bacterium dysenteriae* are present.

steadily in number and after five to six weeks the flora became almost entirely composed of nonsporulating anaerobes.³ Careful examination of the anaerobic plates revealed a progressive predominance of one organism producing grayish raised colonies from 0.5 to 1 Mm in diameter. The blood agar surrounding the colonies was unchanged in the anaerobic state but took on a green color when exposed to air. A foul odor was produced. Stained preparations show this organism to be a gram-negative pleomorphic rod with occasional filamentous forms and irregular staining, but with no true branching and no spores (Figs 4 and 5). It grows only in a strictly anaerobic environment and is easily killed by exposure to oxygen. In one patient with chronic ulcerative colitis several enlarged lymph nodes in the mesentery of ascending colon were removed at the time of the ileostomy and from these the organism was secured in pure culture. It was isolated from the colon of a young girl who died of ulcerative colitis and also from a thrombus in the portal vein at the hilum of the liver. In the patients with ileostomies the organism was, as a rule, easily recovered during periods of acute exacerbation when blood and pus were present in the colon discharge but was not found or only with difficulty, during periods of quiescence. In one of these patients the colon was resected three years after the ileostomy was produced and at this time the organism was still predominant in the diseased colon. It was also isolated together with an anaerobic streptococcus from a mesenteric lymph node in this resected specimen.

We have called the organism *Bacterium necrophorum* because it seems to be identical with the *Bacillus necrophorus* isolated by Bang, in 1890, from cases of calf diphtheria. Bang's organism is well known among veterinarians as the cause of necrotizing lesions in nearly all domestic and in some wild animals, i.e., calf diphtheria, necrotic ulcers of the colon in hog cholera, metastatic necrosis of the liver and lungs of cattle and swine, necrotic stomatitis of calves, lambs, and pigs, and necrotic lesions in the skin of sheep. It is also probably identical with the *Bacillus funduliformis* described by Halle,⁴ Lemerie,⁵ and other French workers, and found to be the cause of ulcerative lesions about the mouth and subsequent often fatal septicemias. Henthorne, Thompson, and Beaver,⁶ of the Mayo Clinic, have isolated *Bacteroides funduliformis* in pure culture from four cases of hepatic abscess secondary to carcinoma of the rectum. This organism seems to be identical with our *Bacterium necrophorum*. Similar organisms have been recovered before from liver abscesses, notably by Harris,⁷ Cunningham,⁸ and Norris.⁹

During the past eight years, *Bacterium necrophorum* has been obtained from about 70 per cent of the patients with chronic ulcerative colitis in our clinic. Two hundred and ninety-eight patients with all stages of the disease have been examined during this period. The organism is difficult to cultivate and a routine technic is not apt to be successful. This is due to the extreme sensitivity of the organisms to oxygen and to the tendency of the fecal bacteria to overgrow the plates. Swabs taken from ulcerated areas by means of the proctoscope and immediately streaked on the surface of 10 per cent sheep blood-veal infusion agar plates, which are then incubated under strict anaerobic conditions, have usually been successful. Our failures to demonstrate *Bacterium necrophorum* in patients with chronic ulcerative colitis have occurred, as a rule, during periods of temporary recovery or quiescence or when it was not possible to make repeated cultures (Figs 6 and 7). Ninety-nine normal individuals were examined with a similar technic but in none of these was *Bacterium necrophorum* found. It was, however, recovered from two patients with carcinoma of the rectum, from one case of lymphogranuloma inguinale, and from one patient with an inflammatory stricture in the sigmoid.

The various strains of *Bacterium necrophorum* isolated from different cases of ulcerative colitis have displayed a similar bizarre morphology and cultural characteristics, but some differences in antigenic properties. Thus, rabbits injected with one strain develop agglutinins to the specific organism injected in much higher concentration than to strains from other sources. Perhaps, the best evidence implicating *Bacterium necrophorum* as an etiologic agent in ulcerative colitis has been the discovery of specific antibodies to this organism in the blood of patients with the disease but not in normal individuals. Both complement-fixing antibodies and agglutinins have been demonstrated. Specific agglutinins for *Bacterium necrophorum* have been found regularly in the blood of ulcerative colitis patients and usually in higher concentration during the active stages of the disease (Table I). In each case, also, a higher concentration of agglutinins for the patient's own strain of

Bacterium necrophorum has been found than for strains from other individuals. This is well illustrated in Table II, where the serum of patient No. 159, in dilutions as high as one in 640, agglutinated strains of *Bacterium necrophorum* obtained from her own colon but had no effect on strains of the same organism from other patients. The presence of these specific antibodies strongly suggests that the organism is actively implicated in the disease process since agglutinins were not found for various strains of *B. coli*, also isolated from the contents of the diseased colon.

TABLE I

PATIENTS* WITH CHRONIC ULCERATIVE COLITIS: CORRELATION OF SEVERITY OF DISEASE AS DETERMINED BY PROCTOSCOPIC APPEARANCE WITH PRESENCE OF *BACTERIUM NECROPHORUM* AND WITH AGGLUTININS FOR *BACTERIUM NECROPHORUM*

Proctoscopic Appearance	Number of Patients	Number from which <i>Bacterium necrophorum</i> Cultured	Number Patients with Agglutinin Titer of 1-40 or Higher for One or More Antigens
0	5	1	1
1	11	2	4
2	18	7	8
3	18	9	13 (one not tested)
4	13	11	9 (two not tested)

Proctoscopic key

0 = healed or normal mucosa

1 = finely granular mucosa—slight contact bleeding in one or several areas

2 = granular mucosa, contact bleeding—areas with no inflammation

3 = bleeding granular mucosa. Little exudate. Areas with less marked involvement

4 = markedly inflamed, bleeding friable mucosa, purulent exudate

* Thirty-six patients were tested; several of them repeatedly, over a period of months during different stages of disease.

TABLE II

AGGLUTININS IN SERUM OF THREE PATIENTS TO HOMOLOGOUS AND HETEROLOGOUS STRAINS OF *BACTERIUM NECROPHORUM*

Patient (Strain)	Date	Proctoscopic Appearance	Agglutinin Titer of Serum for Strains of <i>Bacterium necrophorum</i>					
			103	146	152	159	161	164
H. A. (164)	1/6 /39	1		0		0	0	0
	2/10/39	3		0		40	0	0
	2/24/39	4		0		0	80	80
	6/2 /39	2	0	40	80	0	160	80
L. D. (161)	12/10/38	4				0	80	0
	1/17/39	4				0	80	40
	5/2 /39	4	0	80	160	0	160	40
I. K. (159)	12/20/38	4				640	0	0
	2/14/39	4				160	0	0
	4/4 /39	3	0	0	0	320*	0	0

* Serum not tested above this dilution.

The available data indicate that *Bacterium necrophorum* is pathogenic for both man and the lower animals. Under the names *Bacillus* or *Bacterioides funduliformis* it has been implicated as the causative organism in ulcerated lesions in the throat and metastatic abscesses in distant organs.⁵ We recovered it in pure culture from a chronic breast abscess, and have received cultures of the organism, isolated by others, from a case of osteomyelitis of the femur secondary to middle ear infection, two cases of pleural empyema, and from the blood stream of a patient with lung abscess. We have also

repeatedly isolated it in pure culture from liver abscesses in cattle. The strains of *Bacterium necrophorum* that we have recovered from cases of ulcerative colitis are pathogenic for rabbits, producing in them chronic abscesses on subcutaneous injection. Strains secured from liver abscesses in cattle are more virulent for rabbits than those of human origin and a fatal spreading cellulitis is easily produced. We have, however, been unsuccessful, to date, in reproducing chronic ulcerative colitis in any of the lower animals. Pure cultures of *Bacterium necrophorum* have been given by mouth or by rectal injection, and have been introduced into isolated segments of the colon and lower intestine in dogs, monkeys, and baboons, without the development of any lesions. However, the instillation of a large amount of the bloody purulent discharge from the colon of a seriously ill patient into the same animals was also without effect.

This inability of *Bacterium necrophorum* to set up a colitis under the conditions of our experiments is not surprising in view of some aspects of the epidemiology of the disease. It does not occur in epidemics and is not transmitted even by closest contact. One of our patients, a young woman in whom an ileostomy was performed subsequently gave birth to a healthy baby, and neither husband nor child developed the disease, although the isolated colon of the mother continued to harbor *Bacterium necrophorum* and continued to discharge blood and pus. These observations suggest that the causative agent is not markedly invasive or that some special susceptibility of the host is essential. The excessive chronicity of the disease and its refusal to heal completely even during periods of comparative good health are likewise factors to be considered. Here, too, certain of the properties of *Bacterium necrophorum* appear significant. Beveridge¹⁰ was unable to demonstrate the development of immunity to this organism in rabbits and we have confirmed this observation in a more extensive study.³ Rabbits immunized by repeated injection of *Bacterium necrophorum* developed chronic subcutaneous abscesses as readily and as extensively as the controls. The local necrotizing action of this organism and its failure to incite an increased resistance in the host correspond with the pathology in the colon and the long clinical course of the disease.

SUMMARY

(1) When the seriously diseased colon in patients with chronic ulcerative colitis is isolated from the fecal stream, as by end-ileostomy, aerobic organisms disappear and anaerobic organisms persist in large numbers in cultures secured by swabs or saline washings of the lower sigmoid. Since the isolated colon remains diseased for years, it seems probable that the responsible organism or organisms are anaerobic in nature.

(2) The following evidence indicates that *Bacterium necrophorum* plays an etiologic rôle in the disease.

(a) It is the predominant organism in the isolated colon in ulcerative

colitis during periods of exacerbation and tends to disappear during periods of spontaneous quiescence

(b) It has been found in the great majority of cases of typical ulcerative colitis when appropriate methods for its detection have been used

(c) Specific antibodies for this organism have been found in the blood in cases of chronic ulcerative colitis and not in the blood of normal individuals

(d) The organism is pathogenic for rabbits, producing in them local abscesses and for man as indicated by its isolation in pure culture in a wide variety of pathologic processes

(e) Examination of the literature indicates that it is very similar if not identical with *Bacillus* or *Bacterioides funduliformis* which has been repeatedly found associated with necrotic lesions of the mucous membranes in man and with *Bacillus necrophorus* which is thought to cause various necrotic lesions in domestic animals

(3) *Bacterium necrophorum* is probably present in the normal alimentary tract of man and monkeys and requires some additional factors producing necrosis of the mucosa to furnish conditions suitable for its growth. Once this occurs, the organism seems capable of continuing and extending the process

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DISCUSSION—DR FRANK L MELENEY (New York, N Y) We have been very much interested in the work of Doctors Dragstedt and Dack in this field, and we believe that they have demonstrated the importance of *Bacterium necrophorum* in certain cases of ulcerative colitis. They do not claim that it is the etiologic agent, and I believe that we still have to reserve judgment on that point. I think the fact that they have demonstrated that it persists in the isolated colon after practically all of the other organisms have disappeared is significant. I also believe that the presence in the patients' serum of agglutinins against their own organism, of a higher titre than against other strains of the same species, likewise indicates that at least some of the antigenic properties of the organism have been absorbed from the colon

Of course, in a field which is normally so completely contaminated by many strains of bacteria, as the intestine is, it is very difficult to prove which one, if any, is the significant organism as a causative agent with respect to ulceration of the bowel.

Since Doctors Dack and Dragstedt first published their work we, in our laboratory, have been searching for these organisms in cases of chronic ulcerative colitis. Our habitual search for anaerobes in all specimens that come to the laboratory has also given us the opportunity to find *Bacterium necrophorum* in our cultures from other lesions. Although we have tried very hard to find them in our cases of ulcerative colitis, carefully searching for them in 40 cases which we have examined, we have found them in only three. On the other hand, we have found them in nine other lesions which I would like to enumerate:

(1) In a chronic ulcer of the vagina in a little girl, associated with an anaerobic streptococcus. (2) In a deep pelvic abscess, associated with an anaerobic streptococcus and a *Staphylococcus albus*. (3) In a carbuncle, associated with *Staphylococcus aureus*. (4) In an appendiceal abscess, associated with a colon bacillus, and an anaerobic streptococcus. (5) In a sacrococcygeal cyst, associated with an anaerobic streptococcus. (6) In a thyroglossal cyst abscess, in pure culture, without extensive necrosis of tissue. (7) In a face infection following a dental abscess. (8) In a liver abscess. (9) In a postgastrectomy wound infection.

Doctor Dragstedt has stated that the organism is very susceptible to oxygen, we have confirmed that finding. On account of the probability that anaerobic organisms play a rôle in ulcerative colitis, we have advocated local treatment with zinc peroxide. In the three cases of ulcerative colitis in which we found the *Bacterium necrophorum*, we have had a favorable response to treatment with zinc peroxide. In one of these cases we have been able to keep the disease in a quiescent phase. The patient feels entirely normal with the nightly use of zinc peroxide as a retention enema. In another desperately sick case, rectal administration was not enough. We performed a cecostomy, and delivered the zinc peroxide through the cecum. The disease in the upper large bowel was completely controlled as revealed by a subsidence of symptoms and the restoration of normal contours, as shown by barium enema, but disease persisted in the rectum. A temporary left lower quadrant colostomy was then performed, the fecal stream cut off from the rectum, and this was treated with zinc peroxide, with complete subsidence of the inflammation and healing of the ulcerations. The continuity of the intestine will be restored if the lower segment remains normal for a year.

In the third case, zinc peroxide was delivered through a cecostomy and the upper large bowel was restored to normal. An abdominoperineal operation was performed for persistent rectal involvement and anal fistulae. That patient has remained perfectly well for over three years, with apparent restoration of normal bowel above the level of the colostomy.

I believe zinc peroxide should be considered in treating cases of ulcerative colitis, conservatively at first from below, as a retention enema. If the case does not respond to that, there should be either a cecostomy or in very bad cases, an ileostomy is performed to cut off the fecal stream. If it is delivered from above, serious cases may be restored to normal.

There seems to be a real chance to restore the bowel and avoid an extensive resection. In some cases it may still be necessary to remove the rectum if its mucous membrane has been completely destroyed.

DR LESTER R. DRAGSTEDT (Chicago, closing). I should like to emphasize that *Bacterium necrophorum* is probably identical with *Bacillus funduliformis* isolated by Lemierre and Halle from ulcerative lesions in the nose and throat, with secondary septicaemia and metastatic abscesses in distant organs. It is likely that the organism is a normal inhabitant in the alimentary tract. We have, however, so far been unable to isolate it from the colon of normal individuals. This may be because it is so difficult to isolate and cultivate on the ordinary media. In view of the relatively slight invasive properties of *Bacterium necrophorum*, it seems probable that some other agent may first induce acute ulceration in the colon which is then extended and maintained by the necrotizing properties of *Bacterium necrophorum*. This name seems preferable to *Bacillus funduliformis* because of priority, having been first suggested by Bang, in 1890.

INTESTINAL ANTISEPSIS, WITH SPECIAL REFERENCE TO SULFANYLGUANIDINE*

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BALTIMORE, MD

IN APRIL, 1940, Roblin and his associates¹ described the synthesis and physical properties of sulfanylguanidine before the Division of Medicinal Chemistry at the meeting of the American Chemical Society. These investigators gave the solubility of the compound in water as 190 mg per 100 cc at 37° C. Despite this relatively high solubility, they found that the chemotherapeutic activity as tested in mice, to be considerably less than that of the active sulfonamides. In September, 1940, E. K. Marshall, Jr., *et al.*,² published a report of their experiments with sulfanylguanidine. They had studied its antibacterial properties and its absorbability when given orally and intraperitoneally. They also described their observations on the toxicity of this compound in laboratory animals. These studies led them to conclude

- (1) "Although fairly soluble in water, sulfanylguanidine is poorly absorbed from the intestinal tract
- (2) "The concentration of coliform bacteria in the feces of mice can be reduced by its administration
- (3) "The toxicity of this drug has been investigated in mice, rabbits and dogs. On the basis of all experiments, it would appear, when given by mouth, to be no more, and probably less, toxic than sulfapyridine and sulfathiazole."

Believing that an antibacterial compound, which is fairly water soluble but only slightly absorbed from the intestine, would be of great value in surgery, we gave sulfanylguanidine to 12 patients who required operations upon the colon. The results of this initial study were presented³ at the meeting of the Southern Surgical Association in December, 1940. None of the patients showed detectable evidences of toxicity. In some cases, the fall in the concentration of coliform organisms in the stool was surprisingly great and, although no conclusions were drawn from such a limited experience, the impression was gained that this drug is an adjuvant in colonic surgery. Further clinical experience with the use of this sulfonamide modified the initial impression and made experimental work necessary in order to ascertain the value of this drug in surgery. The results of our studies with sulfanylguanidine can be most conveniently presented under the appropriate headings: (1) Reduction of coliform bacteria in the stool, (2) absorption and excretion of the drug, and (3) toxicity.

(1) *Reduction in the Coliform Bacteria in the Stool*—Our observations upon patients had not progressed very far before it became clear that in some

* Read before the American Surgical Association, White Sulphur Springs, W. Va. April 28-30, 1941.

persons the number of coliform organisms in the stool was unaltered despite the oral administration of sulfanilylguanidine for ten days. The regular dose was 50 mg per kilo of body weight, every eight hours. On the other hand, there were patients in whom the drug produced an impressive reduction in the number of these bacteria in the stool. Similar variations in the response to this drug were observed in dogs, in fact, with twice the dose, *i e*, 50 mg per kilo, every four hours, it was the exceptional animal that had even a moderate lowering in the concentration of the coliform bacteria. When dogs were kept on a low residue diet and given 1 Gm of the drug per kilo per day, in six equal doses by gavage, a marked reduction in the bacterial count usually occurred in

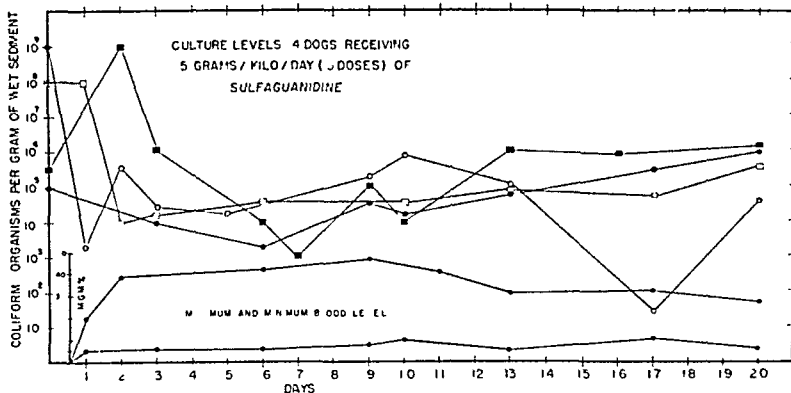


CHART 1—The effect of large doses of sulfanilylguanidine on the number of coliform organisms in the stool of dogs. The maximum and minimum concentrations of the drug in the blood are shown.

from five to eight days. There were some dogs, however, under this regimen that failed to show a definite reduction, and a further increase in the dose would sometimes, but not always, cause a significant lowering in the number of bacteria in the feces. There were many animals that survived the incredibly large dose of 5 Gm per kilo per day for more than a month. Chart 1 illustrates the course of four such dogs. It is seen that the concentration of coliform organisms is gradually reduced to a level varying from 10,000 to 100,000 organisms per cc of wet sediment of stool, and that further reduction is not attained by continued administration of the drug.

On theoretical grounds, if the bacteriostatic effects of sulfanilylguanidine are due entirely to the action of the drug on the contents of the bowel, then it follows that the maximum effect should be expected when saturation of the intestinal contents is reached. In an effort to throw light on this point, the concentration of sulfanilylguanidine in the stool was determined and correlated with the bacterial count. No relationship could be established because the stool always contained solid drug if more than 0.5 Gm per kilo per day was given by mouth, and it was found that this was the minimum amount required to lower the bacterial count. In dogs which received enormous amounts of the drug by mouth, the feces would be almost solid with sulfanilylguanidine, yet, 1 cc of the wet sediment of such a stool frequently contained over 100,000 coliform organisms.

The bacterial count in the stool may not represent an accurate indication of the action of sulfanilylguanidine within the colon. It seems that the repeated analysis of the contents of isolated segments of colon that contained the drug

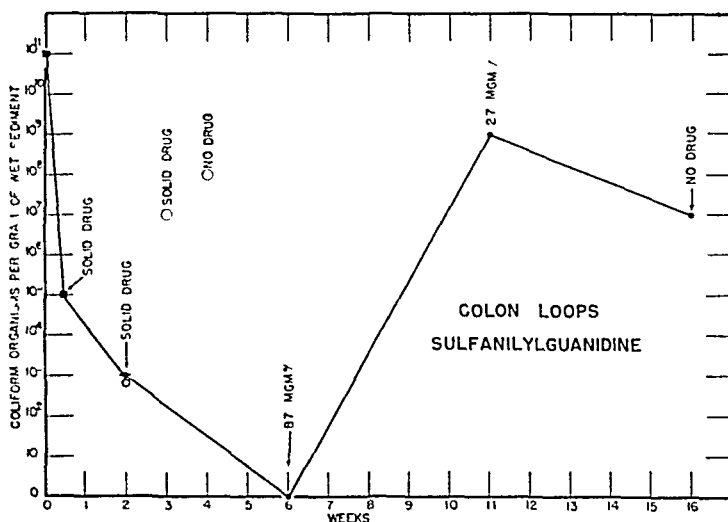


CHART 2A—The rate of absorption and the bacteriostatic effect of sulfanilylguanidine when placed in isolated colonic loops

might give more reliable data. Our next experiment was planned to do this and also to compare the antibacterial effect of sulfanilylguanidine and sulfanilamide under standard conditions.

For this purpose, identical segments of the colon of dogs were isolated and the continuity of the bowel was restored by anastomosis. From each isolated segment the gross fecal matter was washed away, specimens for bacteriologic study were taken, and 5 Gm of either sulfanilamide or sulfanilylguanidine were placed in the lumen of a loop before closure was completed. Subsequently, the peritoneal cavity was opened and the contents of the loop were aspirated under aseptic precautions.

The samples thus obtained were studied to determine (1) the concentration of the drug remaining in the loop, and (2) the effect of each compound on the bacteria within the loop. The values found in these determinations are given in Chart 2 A and B. Under the conditions of this experiment it is evident that each compound caused a pronounced decrease in the number of coliform bacteria within the lumen of the isolated segments of colon. The fall in the number of bacteria extended from over a billion organisms per cc to less than ten. In every instance, the bacteriostatic effects disappeared when all the drug had

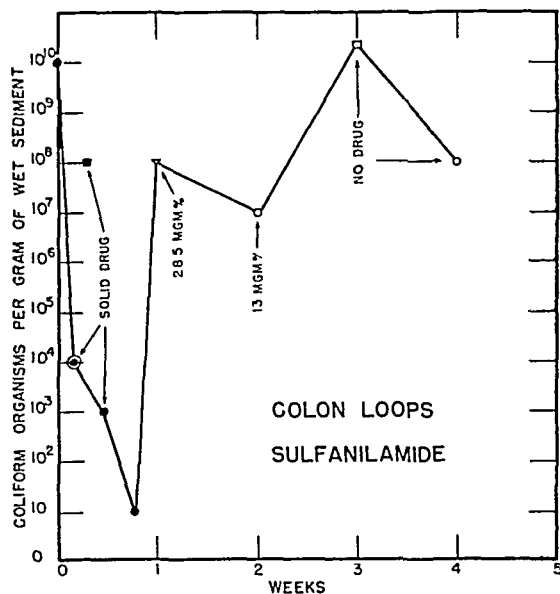


CHART 2B—The rate of absorption and the bacteriostatic effect of sulfanilamide when placed in isolated colonic loops

been absorbed from the loop. From the charts, it is clear that the rate of absorption of sulfanilamide from the isolated colonic loop is very much faster than that of sulfanilylguanidine. Histologic examination of the isolated segments of the colon did not show any alteration because of their prolonged contact with these drugs.

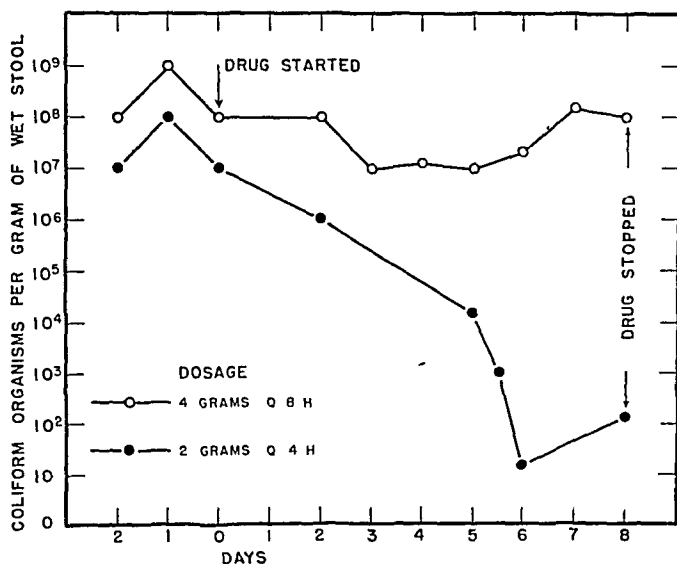


CHART 3—The action of sulfanilylguanidine on the bacterial flora of the normal gastro-intestinal tract of man when given at four and eight hour intervals

The frequent failure of sulfanilylguanidine to reduce the number of coliform bacteria in the stool might be explained on the spacing of the doses. To investigate this possibility, we gave a group of normal adult men 4 Gm of the drug by mouth every eight hours, and a second similar group 2 Gm of the drug by mouth every four hours. Chart 3 illustrates the differences resulting when the more frequent doses were given. It will be noticed that after eight days of treatment with an eight-hour interval, the bacterial count was scarcely altered, whereas within six days with an interval of four hours between the doses, the count fell from 10,000,000 to less than 100 organisms per cc of stool. The greater effectiveness of frequent doses was also shown in dogs. A typical illustration is given in Chart 4, wherein the maximum effect of sulfanilylguanidine was obtained in four days when the drug was given at four-hour intervals. In contrast to this, the fall in the number of bacteria was slower and less marked when the doses were spaced at 12-hour intervals. The explanation which is offered for the greater effectiveness of the drug when administered frequently is that by shortening the interval between doses, more constant contact is maintained between the drug and the mucous membrane harboring the bacteria.

In an effort to determine why some patients showed a reduction in the bacterial count, whereas others on the same dietary regimen and dosage of sulfanilylguanidine showed no reduction, we studied the records of 48 patients

treated with the drug. From this study, it was evident that the patients with an ulcerative carcinoma in the colon showed little or no fall in the number of bacteria in the stool (Chart 5). This was consistently true and, although the number of patients with ulcerative lesions is less than 20, it is important to learn whether this observation is confirmed. If it is true that an ulcerative lesion in the bowel neutralizes the bacteriostatic activity of sulfanilylguanidine,

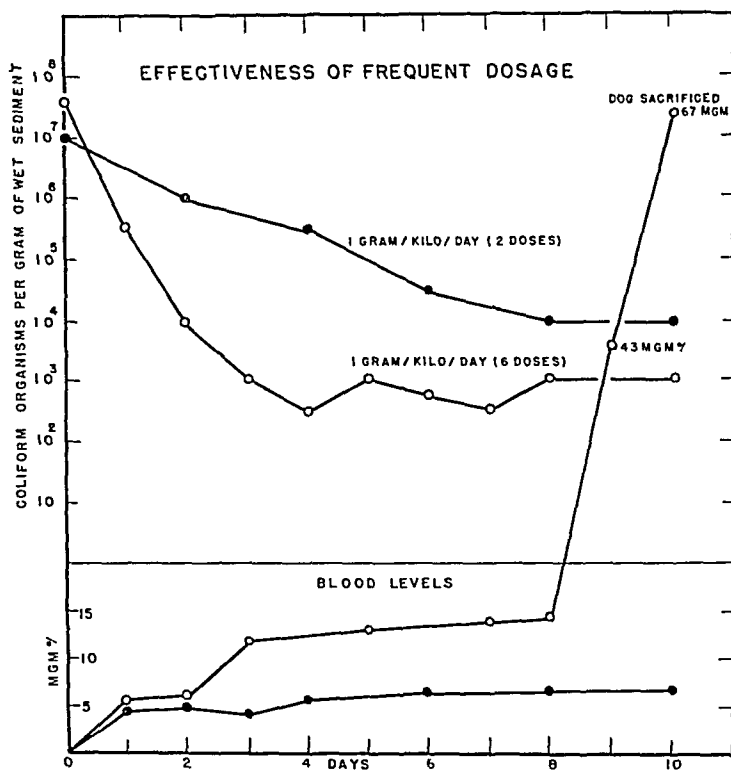


CHART 4—The action of sulfanilylguanidine on the coliform bacteria in the gastrointestinal tract of dogs given at four and 12 hour intervals. The corresponding concentrations of the drug in the blood are given.

this fact will constitute a real limitation to the use of the drug in surgery. It is well known that purulent exudates contain an antisulfonamide factor which renders this compound ineffective. The suggestion is made that infected carcinomata in the bowel may produce a similar antisulfonamide factor. In our group of patients, extensive reduction in the number of coliform organisms was obtained only in those whose intestinal mucosa was intact. It was in these patients that the bacterial counts fell from over 10,000,000 to less than 1,000. If, when resecting the colon, enormous reductions are dependent upon an intact mucous membrane, surgeons may prefer a two-stage operation, in which the ulcerative lesion is removed by the Mikulicz procedure, and sulfanilylguanidine given to reduce the bacterial flora before the continuity of the bowel is restored. If sulfanilylguanidine, or a similar sulfonamide compound, can be relied upon to render the colon relatively free of pathogenic bacteria, the bowel can then be anastomosed and returned to the peritoneal cavity.

(2) *Absorption and Excretion of the Drug*—Our experiments indicate that sulfamylguanidine is more slowly and less completely absorbed from the intestinal tract than many other compounds of the sulfonamide series, but it has become clear that the low concentration of the drug in the blood is not due primarily to poor absorability but rather to its prompt elimination by the kidneys. This fact is supported by the observations of Marshall and his associates,⁴ who found that a dog receiving 0.02 Gm per kilo of the drug by mouth had excreted 37.7 per cent after four hours, and 52.2 per cent after six hours. In a patient who received 2 Gm of sulfamylguanidine every four hours, the

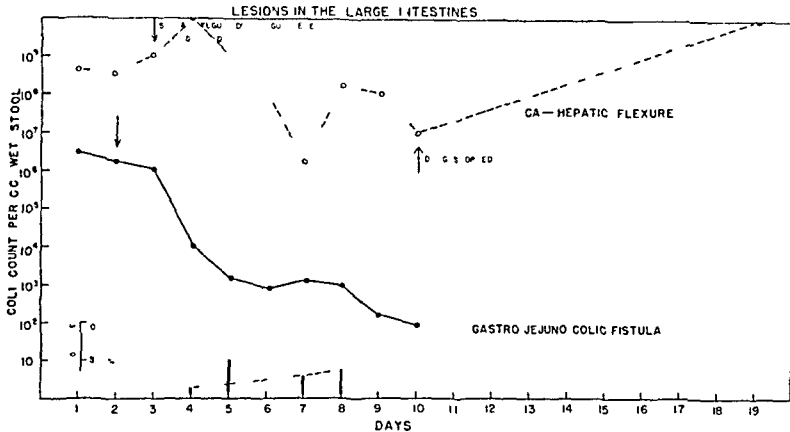


CHART 5—The effect of sulfamylguanidine on coliform organisms in the presence of ulcerating lesions (carcinoma of the hepatic flexure) is compared to the effect when the mucosa is intact (gastrojejunal colic fistula)

blood level varied from 2 to 69 mg per cent. On the fourth day, the total urinary output was 4.4 Gm, and during the following 24 hours more than 50 per cent of the ingested drug was excreted by the kidneys (Chart 6). Within one day after withdrawal of the drug, the renal output of sulfamylguanidine fell to 0.05 Gm, although a considerable quantity of the drug was still in the lower colon. This bears out Marshall's⁴ experiments, which showed that sulfamylguanidine is absorbed from the small intestine more rapidly than from the large, and that it is promptly excreted in the urine. In this communication, dealing with the use of the drug in bacillary dysentery, it is pointed out that in one patient who received 0.05 Gm per kilo every four hours, the average urinary excretion of the drug was 13 per cent of the amount ingested. In a second patient, on the same dosage, the average excretion was 25 per cent. It is noteworthy that these patients (Cases 5 and 7), were having diarrhea, and that the patient with the 25 per cent urinary excretion was having from seven to ten stools a day.

It must be emphatically stated that absorption from a diseased intestine, or in the presence of intestinal obstruction, is unpredictable. To demonstrate this, the following experiment was performed. The terminal ileum of dogs was divided and occluded. One gram of sulfamylguanidine per kilo was introduced into the intestine above the obstruction. The results in the blood levels varied from 3 to 350 mg per cent. The animal which showed the latter figure

died within four hours. In patients with actual or impending intestinal obstruction, the use of sulfanilylguanidine is contraindicated, for not only is the absorbing function of the intestine greatly altered but the occurrence of reversed peristalsis tends to retain the drug in the small intestine, where it is readily absorbed.

In several of the animal experiments, in which from 1 to 5 Gm of sulfanilylguanidine per kilo were administered each day over a period of weeks, a sudden increase in the concentration of the drug in the blood occurred. An illustration of this complication is shown in Chart 4. Whether this is due to an alteration in the rate of absorption or excretion of the drug is not clear, but the latter seems more probable. Similar observations have

not been made in patients, but, on the other hand, the drug was always withdrawn on the first evidence of toxicity. It seems likely that, with the customary therapeutic dose of sulfanilylguanidine, patients with severe renal disease or those having anuria following anesthesia, might develop excessively high blood levels. It is imperative, therefore, that the renal function of a patient be fairly normal before he receives this drug.

(3) *Toxicity*—It is not fair to make any deductions concerning the toxicity of sulfanilylguanidine in dogs which received 5 Gm per kilo per day. It is significant, however, that several dogs survived this enormous dosage for 50 days—a fact which argues strongly for the relatively low toxicity. None of the original 12 surgical patients who received sulfanilylguanidine showed any signs of toxicity, but in the subsequent 36 patients four had mild toxic symptoms. Three of these four patients received the drug at four-hour intervals. The manifestations of toxicity were fever (four cases), erythematous rash (two cases), headache (two cases), anorexia and nausea (four cases), photophobia (one case), and conjunctivitis (one case). In every instance, the toxicity promptly disappeared upon the withdrawal of the medication. None of our patients developed hemolytic anemia, jaundice, hematuria, leukopenia, or granulocytopenia.

Apparently, the toxicity bears no relationship to the concentration of the

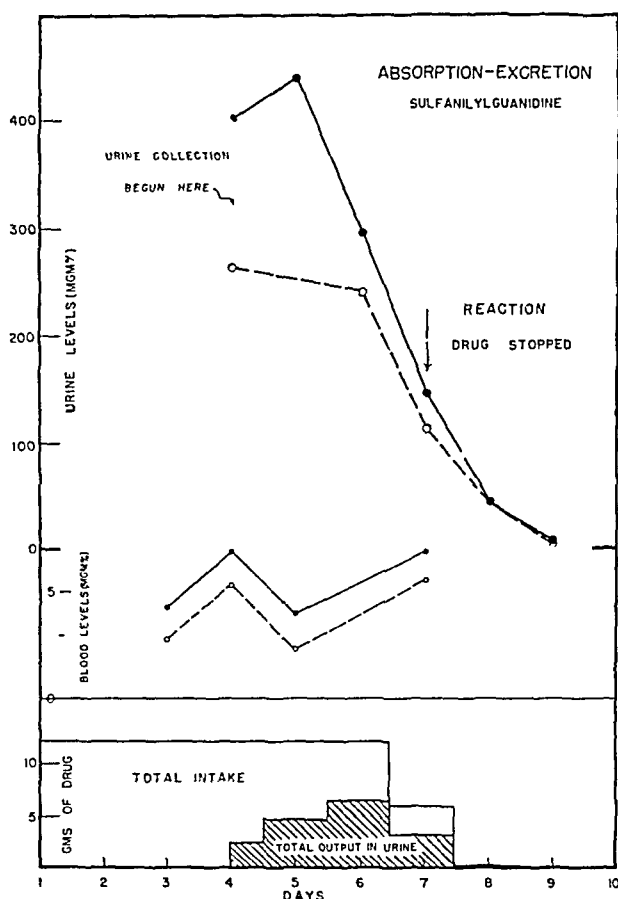


CHART 6—The rates of absorption and excretion of sulfanilylguanidine by a patient with a normal gastrointestinal tract receiving two grams of the drug every four hours.

drug in the blood, but may be associated with the quantity of the drug absorbed and excreted. If 6 Gm of the drug are excreted in 24 hours, and 40 per cent of the compound is conjugated, and the acetyl derivative has a solubility of 75 mg per cent in urine, it would require an urinary output of 3,200 cc to keep the acetyl derivative in solution, and thereby insure against the formation of crystals in the upper urinary tract.

It seems probable that toxic reactions of serious proportions can be avoided if certain precautions are followed. First, sulfanilylguanidine should not be given to patients with seriously impaired renal function. Second, the drug should be discontinued upon the first evidence of toxicity. Finally, the daily urinary output must be kept above 1,500 cc.

SUMMARY AND CONCLUSIONS

Experimental and clinical studies with sulfanilylguanidine have shown that when an adequate amount of the drug is given at sufficiently frequent intervals, the coliform flora of the bowel can usually be significantly reduced. This treatment does not decrease the number of other bacteria in the colon. No reduction in the number of coliform organisms has been obtained in the presence of ulcerative lesions of the bowel.

Although the drug is slowly absorbed when taken by mouth, a considerable quantity of the compound is absorbed under therapeutic conditions. Ordinarily, concentration in the blood remains low because the drug is rapidly eliminated in the urine. Abnormalities of absorption or excretion may cause a dangerous accumulation of the drug in the body.

Relatively mild toxic reactions have occurred in patients receiving sulfanilylguanidine by mouth. The more severe reactions caused by some of the other active sulfonamides have not occurred. Apparently, there is no relationship between the toxicity and the concentration of the drug in the blood. To avoid serious reactions, sulfanilylguanidine should not be given to patients with intestinal obstruction or with seriously impaired renal function, and should be withdrawn immediately upon the appearance of toxicity.

The authors thank Drs. F. Louis Knotts and Frank Inui for their assistance.

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DISCUSSION.—DR HARVEY B. STONE (Baltimore, Md.) I shall limit my remarks to my own personal experience in the use of this drug. First, I would like to mention one

phase of its possible value which Doctor Firor did not touch upon in his paper. We have employed it in some six or eight cases of chronic ulcerative colitis, in the hope that it might prove of value in the treatment of this disease, and I regret to say that, so far as this scanty evidence goes, it proved to have no beneficial effect whatever, that we could recognize. It simply did nothing toward relieving the symptoms or improving the appearance of the mucous membrane in the bowel, as seen through the proctoscope.

I have used the drug as a preparatory measure in 25-odd cases in which the operation was planned upon the large bowel for one cause or another, and can report that in that series of cases there were no deaths as a result of the operation which followed this preparatory treatment. I think, however, that this is entirely negative evidence, because it is not at all unusual to run a series of 25 cases with the ordinary preoperative preparation, lacking sulfamilylguanidine, without a fatality, so that this evidence I think is of no great value.

In this group of cases, I had one patient who showed very much more severe toxic symptoms than those which Doctor Firor has reported in his experience. This patient ran a sudden elevation of temperature from a previous level of perhaps a maximum of 100° F in the 24-hour chart, to an elevation of 103° F, with a pulse rate increasing from approximately 100 to 140, with coma, cyanosis, and had the general appearance of desperate illness. The drug was immediately stopped, and within 24 hours all of the symptoms completely disappeared, so that I think it is a fair assumption that this grave change in the patient's condition was actually a toxic manifestation of sulfamilylguanidine.

In conclusion, the evidence that I have so far acquired personally from the use of this drug has not been such as to lead me to think it has great value, and I have, personally, discontinued its employment as a preoperative preparatory measure for resections of the large bowel.

DR HERMAN E. PEARSE, JR (Rochester, N. Y.) I would like to ask Doctor Firor if he has used the drug in the treatment of regional ileitis or regional enteritis. We have, with a very slight experience, gained the impression that it may be valuable in at least controlling the symptoms in patients with this disorder who have extensive disease beyond the possibility of resection.

DR WARFIELD M. FIROR (Baltimore, Md., closing) In answer to Doctor Pearce's question, I should say we have used sulfamilylguanidine in only one instance, with questionable benefit.

I think that I can quickly summarize our feeling about this compound. First, to gain any lowering in the concentration of the coliform bacilli in the stool, it is necessary to give the drug at four-hour intervals. Second, in the presence of ulcerative lesions, it seems to be ineffectual, and if this observation is generally confirmed it indicates a real limitation in the use of this compound.

We feel that the drug is absorbed in large quantities, but slowly, from the alimentary canal, and promptly excreted by the kidneys. Where there is a diseased bowel or impending or actual intestinal obstruction, the drug should not be employed. We believe that there will be an increasing number of reactions with the closer spacing of the doses.

Finally, I think we can summarize our feeling, as I did at the Southern Surgical Association, by saying that we do not think sulfamilylguanidine has great merit of its own, and that its chief value is that it points the way to a new approach for making surgery of the large bowel safer.

THE SYNDROME OF MESENTERIC OR SUBPERITONEAL HEMORRHAGE (ABDOMINAL APOPLEXY)*

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RUPTURE of intra-abdominal blood vessels in the absence of aneurysm or of direct major violence appears to be extremely rare. We have found but 18 reported cases, in only one of which (Crile and Newell) was the diagnosis made before operation or necropsy. We report three additional cases, bringing the total to 21, and in one of these there were two hemorrhages, two years apart—the only instance we have found of repeated, unconnected episodes of mesenteric apoplexy. From a study of these new cases and of the few previously reported, in sufficient detail, we believe it is possible to recognize a series of signs and symptoms, correlated with the progressive stages of such hemorrhages—a syndrome often sufficiently clear to permit clinical diagnosis.

CLINICAL PICTURE

(1) *Age, Sex, and Vascular Condition*—Mesenteric vascular rupture has occurred about twice as often in males as in females. The average age was 53, with only three patients under 40, the youngest 27. Arteriosclerosis, either demonstrated or presumed on account of age, was present in four-fifths of the cases, and well-marked hypertension in one-third.

(2) *Injury or Strain*—These shortly preceded the onset of symptoms in each of our three patients, though in two the strain was relatively minor (being “jerked” when boarding a moving street car, carrying a heavy load of commuter’s bundles on to a ferry). The patients were little impressed by these incidents, the histories being obtained only by persistent, direct questioning, and this may account for the fact that in only one of the previously reported cases was strain or injury recorded.

(3) *Character of Initial Pain*—A fresh hematoma, confined between mesenteric leaves or spreading under visceral peritoneum, gives rise to the characteristic *dull, sickening pain* of peritoneum under tension. It is usually sudden in onset, persistent or gradually subsiding, rather than intermittent and colicky, as in obstruction, and is usually accompanied, sooner or later, by nausea and vomiting. Instead of the tense quiet of peritonitis, patients exhibit a restless and unsuccessful search for a position of comfort. Vomiting and evacuation of the bowel afford no relief.

(4) *Subsidence and Recurrence of Pain*—If hemorrhage ceases, distress gradually subsides, only to return if the size of the hematoma is increased.

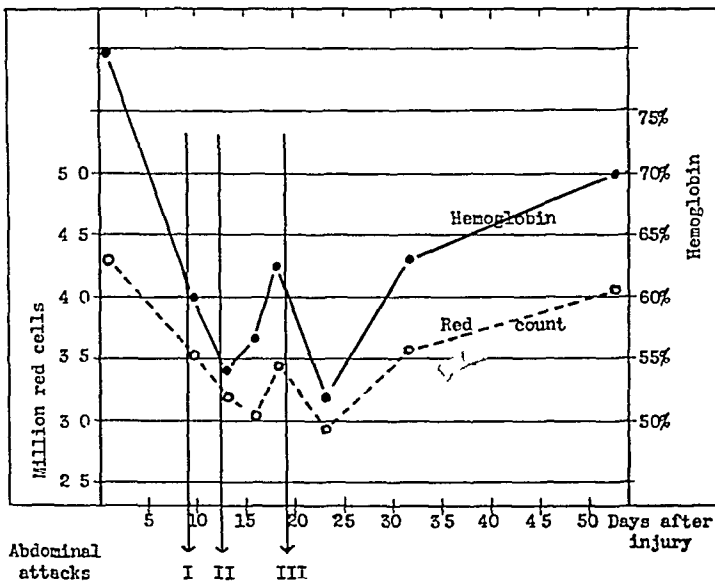
* Read before the American Surgical Association, White Sulphur Springs, W. Va., April 28-30, 1941.

by renewed bleeding This *fading and return of pain* occurred in seven of the cases reported in the literature and in each of our three patients

(5) *Secondary Severe Pain and Shock*—With continued bleeding, rupture of a leaf of mesentery encapsulating the hematoma occurs and blood under tension is suddenly poured out into the peritoneal cavity This produces *sudden, excruciating exacerbation of pain* followed rapidly by *collapse* with lowered blood pressure, clammy skin, rapid thready pulse and subnormal temperature

Physical activity, vomiting, or the use of purgatives may increase or re-establish bleeding, and so be responsible for increase or recurrence of symptoms

Time from initial pain to rupture into the abdominal cavity has varied from an interval too short to permit recognition of the symptoms of hematoma up to several days In Silvertone's patient, the symptoms subsided after three days and returned two or three times before sudden collapse a week later Bruce's patient had vague abdominal pains two days before his general peritoneal signs Morton reported a clear example of repeated bleeding for a week before rupture of the hematoma In our first case, onset occurred 24 hours before rupture into the abdominal cavity There was temporary



CASE 3
Red counts and hemoglobin estimations

CHART 1

subsidence of distress, exacerbation following eating, and again after taking castor oil Rupture of the hematoma finally occurred during induced vomiting Doubtless, subperitoneal hemorrhage has occurred in many instances without rupture into the general cavity, thus escaping operation and diagnosis

(6) *Leukocytosis*—The white count is usually elevated In our cases, counts ranged from 11,600 and 12,700 with unruptured hematomata to 21,000, 24,000 and 26,000 with hemoperitoneum

(7) *Red Count and Hemoglobin*—If hemorrhage of considerable quantity occurs, ceases, and is renewed at long enough intervals to allow compensatory increase in blood volume, hemoglobin and red count will be reduced (see chart of Case 3)

Treatment—In 17 patients operated upon, the source of bleeding was said to have been identified and ligated in seven, with but one death. Of ten cases in which no point of hemorrhage was located, four died. This suggests that operation is the treatment of choice. Yet it may well be that in some instances it was possible to identify and ligate bleeding vessels because of the fact that hematomata were less massive and extensive and that several of these patients might have recovered equally well without operation. Of the four instances (in three patients) reported here, recovery followed in two, without operation, and in two, after operation, at which nothing was done directly to stop bleeding.

If clinical diagnosis can be made, the duration and severity of symptoms may be a better guide to treatment than an invariable decision to operate upon all patients. If bleeding is slow or intermittent, expectant treatment with complete rest of the patient and his gastro-intestinal tract may well be indicated. If the period of time from onset to rupture of the hematoma is short, indicating rapid hemorrhage, prompt operation is obviously the treatment of choice.

CASE REPORTS

Case 1—Male, age 40, steel worker. Shortly after dinner, this man ran a block or more and boarded a car after it had started. He received "quite a severe jerk" when he caught the hand rail but felt no abdominal pain at the moment. Ten or 15 minutes later, while sitting in a theater, dull pain began in his upper abdomen, constant, gradually increasing in severity. He felt an impulse to have a bowel movement, but a fairly large evacuation gave no relief. He left the theater and returned home because of increasing pain.

Discomfort was severe enough to keep him from sleeping that night but subsided toward morning. Immediately after eating a light breakfast, the same nagging, persistent pain in the epigastrium returned, and remained with moderate severity throughout the day while he rested at home. By evening it had lessened and he ate a fairly heavy dinner, followed by another exacerbation of distress. A large dose of castor oil served only to increase pain. By this time there was a little nausea. Vomiting was induced by gagging, during which the pain suddenly became agonizing throughout the entire upper abdomen and he felt as if a belt were being tightened about his waist.

One of us (G. F. C.) saw him about ten minutes later. He was moaning with pain, incessantly tossing about in bed, unable to find a position of even relative comfort. Pulse 120, thready and barely perceptible, blood pressure 70/50, skin clammy and cold, temperature 95.6° F. The abdomen was moderately tender throughout on deep pressure, but without rigidity or even localized muscle spasm. At hospital, an hour later, WBC 26,000, 67 per cent polymorphonuclears. The patient was now vomiting small amounts of bile-stained fluid at frequent intervals, with no relief of exquisitely acute pain.

Tentative Diagnosis Mesenteric thrombosis.

Operation—Upon opening the abdomen, under novocain, through an upper right rectus incision a large quantity of dark blood gushed out. The transverse mesocolon was distended by an hematoma between its leaves extending from root to colon and

from hepatic to splenic flexures. There was a rent in the lower surface of the mesocolon, through which blood had escaped, but the tear was filled with clot and no active bleeding could be found. The hemorrhage was presumably from a branch of the middle colic artery. There was no evidence of inadequate blood supply to the transverse colon. The abdomen was closed without drainage, and 100 cc of whole blood injected intramuscularly.

Convalescence was uneventful. He was discharged from hospital in three weeks, and returned to work as a structural iron worker at the end of two months.

No cause for the hemorrhage could be determined, unless it was the seemingly insignificant injury of a "jerk" when boarding a moving street car. He had no appreciable thickening of peripheral arteries and blood pressure on several occasions was within normal range. Wassermann test was negative.

He remained well for two years. Then, about two hours after eating, without injury or strain, he suffered another attack of dull epigastric pain. It was not, at first, severe enough to prevent him from going to work but persisted and gradually increased in severity so that he had to quit and go home after a few hours. He described his pain as dull, "dragging" or "tearing" in character, constant and not intermittently cramping—the same, he said, as that in the attack two years before. A dose of castor oil was followed by vomiting, but this time no sudden major exacerbation of pain with shock and collapse followed.

The abdomen presented only a moderate degree of diffuse tenderness in its upper half. There was no muscle spasm and no mass was felt, either at first examination or later. Temperature 100° F, pulse 94, W B C 12,700, with 85 per cent polymorphonuclears, hemoglobin 95 per cent, R B C 4,550,000. Intramuscular injection of whole blood was administered twice, and he was kept at rest and without food for 24 hours. Pain, fever, and leukocytosis subsided over a period of three days, and he was discharged with diagnosis of recurrence of mesenteric hemorrhage, not going on to rupture of the hematoma.

At recent physical examination, five years later, he was found in good health, having worked steadily and with no recurrence of abdominal distress.

Case 2—Female, age 63, stenographer. She had had repeated attacks of epigastric pain over several years, diagnosed as cholecystitis but without jaundice or fever. She had had one attack of transitory vertigo a few months before present illness.

While carrying a considerable load of week-end supplies on to the ferry, she suddenly "felt as if something tore on each side, right from chest to abdomen." This pain lasted only a few seconds, she continued her trip, remained active and had no further distress during the rest of the day. In the afternoon of the following day, she began to have colicky pains across the lower abdomen, gradually increasing in intensity and finally becoming constant. An hour after the second onset she had nausea and then severe, repeated vomiting. The second morning she was still suffering pain and nausea. There was no fever, hemoglobin 94 per cent, R B C 5,130,000, W B C 11,600, 78 per cent polymorphonuclears, urine normal. Flat roentgenogram of the abdomen showed moderate distention of several loops of small intestine, suggesting at least partial obstruction.

At operation, in the evening of this second day of illness, a subperitoneal hemorrhage was found, extending from the base of a small, noninflamed Meckel's diverticulum eight inches toward the cecum, spreading under the peritoneum of the bowel rather than in the mesentery. The diverticulum was inverted with purse-string suture, though no active bleeding could be found. Recovery was uneventful.

This patient's peripheral vessels were not unusually hardened and her blood pressure was within normal limits. She died, however, five years after this incident from cerebral hemorrhage.

Case 3—Male, age 51, bridgeworker. A rather heavily loaded supply car with steel-flanged wheels ran over his left thigh near the groin. He suffered an extensive

abrasion and contusion of the thigh, most severe on the mediodorsal aspect. The scrotum was contused and both testes swollen. The abdomen was soft, not tender, and presented no external evidence of injury. There was no fracture of pelvis or spine nor any bladder injury. Peripheral arteries were moderately thickened, blood pressure 125/60, W B C 21,250, with 96 per cent polymorphonuclears, hemoglobin 80 per cent, R B C 4,320,000.

His progress was satisfactory until the ninth day, when his temperature rose to 102.2° F. He complained of persistent, extremely annoying, dull ache about the umbilicus with a little nausea but no vomiting. On this day W B C was 24,000, hemoglobin 60 per cent, R B C 3,500,000.

The abdominal symptoms gradually subsided and he felt fairly well the following day. Two days later a similar episode occurred, subsiding this time in about 36 hours. White count during this attack was 19,200, hemoglobin 57 per cent, red count 3,040,000.

No further discomfort was complained of until another full week had elapsed. Red count had risen to 3,460,000, with hemoglobin 65 per cent. The third attack was identical in character with the two preceding ones—the same annoying, constant, aching pain centered around the umbilicus, associated with slight nausea. Repeated abdominal examinations demonstrated no tenderness, muscle spasm nor any mass. Hemoglobin after onset of the third attack dropped to 52 per cent, R B C 2,900,000, W B C 18,300.

The character of pain and its recurrence, associated with leukocytosis, afebrile except at first onset of pain, with such definite reduction in hemoglobin and red count (see chart) following each episode, led us to a diagnosis of subperitoneal hemorrhage, intermittently renewed but with hematoma unruptured into the general cavity. It was not until about one month later that a vaguely definable mass was first discovered in the right lower quadrant. It was about the size of a grapefruit, not tender and gave the impression of containing fluid. The patient had, by this time, no complaints that could be referred to it. Gastro-intestinal roentgenograms were reported as showing "a tumor mass in the right lower quadrant which does not invade the bowel but slightly displaces the cecum and terminal ileum."

The mass gradually diminished in size during the following two months while he was under observation. From its location, the hematoma presumably arose from a branch of the superior mesenteric artery. Although the first symptoms suggesting intra-abdominal hemorrhage did not appear until the ninth day following injury, it seems not improbable that the initial vascular rupture occurred at that time and that the more severe pain of the external injuries masked any abdominal distress. Each of the episodes of onset and subsidence of pain apparently represented transitory renewal of bleeding, which finally ceased without peritoneal rupture.

SUMMARY OF COLLECTED CASES

Available information about collected cases (including those herewith reported) is summarized in Table I.

Bleeding came from the distribution of the celiac axis in eight instances and the superior mesenteric in 12—source not identified in one.

In seven cases, the hematoma remained unruptured into the abdominal cavity, in the remainder, hemoperitoneum was found. In all but two of the latter, rupture of the hematoma gave rise to the characteristic clinical picture of profound collapse and shock. Roughly, about one-third began with pain and did not go on to collapse, about one-third began with pain, and after a period of several hours to several days, with or without intervening exacerbations, finally suffered rupture of hematoma into the abdominal cavity with

collapse, and in about one-third, peritoneal rupture occurred so early that collapse and shock were almost initial symptoms

In this small group of cases, every patient age 50 or less (except our Case 1, in his second attack) suffered rupture of the hematoma and hemoperitoneum

Some degree of tenderness was usual, but muscle spasm appears to have varied from none at all to board-like rigidity whether or not hematomata had ruptured

In the hematoma stage, a mass was felt in but two cases, and in one of these (our Case 3) not until three or four weeks after subsidence of symptoms

Operation was performed for 17 of 22 hemorrhages (in 21 patients), with mortality of five (30 per cent), two were diagnosed clinically and recovered without operation (our Cases 1 and 3), three were diagnosed only at necropsy. Total mortality of the reported cases was, therefore, 37 per cent. However, some of the cases contributing to this high mortality were in advanced stages of cardiovascular disease, one or two already in hospital with hemiplegia or essential hypertension, and in some of these, the abdominal hemorrhage was doubtless only a terminal incident rather than a major factor in fatality

SUMMARY

(1) Four new instances (in three patients) are added to 18 previously reported cases of mesenteric apoplexy

(2) A clinical syndrome is described of signs and symptoms correlated with the progressive stages of hemorrhage. Usually in the presence of vascular deterioration, with or without injury or more or less strain or exertion, there occurs dull, "dragging," "pulling" or "tearing," often severe, persistent and increasing abdominal pain—the pain of peritoneal tension—later gradually subsiding but often recurring with renewal of hemorrhage, exacerbated by eating or by vomiting or catharsis, with leukocytosis and, if time permits, drop in red count and hemoglobin, and, finally, if the hematoma ruptures, sudden, severe pain, with shock and collapse

(3) In two instances, we believe the clinical diagnosis was justified, although this was not confirmed because of recovery without operation

(4) One patient suffered recurrence two years after the initial episode. This appears to be the first such case reported

(5) Treatment is discussed, and it is suggested that decision for or against surgical intervention should depend upon the apparent rate of bleeding or the occurrence of early rupture into the abdominal cavity

Since this paper was submitted, an additional case has been reported as intra-abdominal apoplexy, though no source of bleeding was demonstrated on extensive exploration (Berk, J. E., Rothschild, N. S., and Doane, J. C. Intra-abdominal Apoplexy. *ANNALS OF SURGERY*, 113, 513-520, April, 1941)

TABLE
SUMMARY OF

Author	Age	Sex	Etiologic Factors	Source of Bleeding	Duration of Symptoms	Number of Exacerbations After Onset	Collapse and Shock	Tenderness
Budde	27	M		Left gastro epiploic	6 hrs		0	++
Florence and Ducuing	30	F	In labor	Sup mes	48 hrs	0		
Hartley and MacKechmie	31	M		Sup mes	12 hrs	1	0	0
Bruce	34	M		Sup mes	48 hrs	1	Secondary	+
G F C A R K Case 1	40	M	Mild trauma	Right colic	24 hrs	4	Secondary	+
Same 2nd attack	42	M	0	Same?	24 hrs	0	0	+
Moorehead and McLester	44	M	B P 220/140	Celiac axis	? (sudden death)		Initial	
Hillhard	48	M	Hemiplegia hypertension	Sup mes	1 hr	0	0	
Crile and Newell	49	F	Essential hypertension	Middle colic	3 hrs	0	Initial	+
Moorehead and McLester	50	M	C-V Dis	Sup mes	? (sudden death)		Initial	
G F C A R K Case 3	51	M	Trauma	Sup mes	2-3 weeks	3	0	0
Silverstone	52	M	C-V dis	?	1 week	5	Secondary	+++
Green and Powers	54	F	B P 230	Left gastric	5 hrs	0	0	++
Mourgue Molines and Cabanac	56	M	Arterio sclerosis	Right gastric	? 48 hrs	? 1	? Secondary	0
Buchbinder and Greene	57	M	Arterio sclerosis B P 190	Right gastric	5 hrs	0		++
Starcke	60	M	Arterio-sclerosis	Gastro duod	2-3 days	1	Secondary	++
Thompson and Dunphy	62	F	Hemiplegia hypertension	Celiac axis	18 hrs	0	Initial	
G F C A R K Case 2	63	F	Arterio-sclerosis	Sup mes	2 days	1	0	++
Bruce	72	M		Middle colic			Initial	++
Morton	72	M		Sup mes	6 days	2	Secondary	
Mourgue Molines and Cabanac	73	F	Hemiplegia	Left gastro epiploic	Few hrs	0	0	
Cutler	80	F	Arterio-sclerosis hypertension	Right colic	24 hrs		Initial	+++

ABDOMINAL APOPLEXY

I

COLLECTED CASES

Rigidity	White Count	Unrup- tured Hema- toma	Hemo peri- toneum	Bleed- ing Vessel Lig- ated	Bleed- ing Vessel Not Found	Not Oper- ated	Recov- ered	Died	
+++			+	+			+		
+++			+			+		+	Autopsy diagno- sis Gangrene of bowel
+			+		+			+	
+	26,150		+		+		+		
o	12,700	+				+	+		
			+			+		+	Autopsy diagno- sis
+++			+		+			+	
+			+	Bowel resected			+		Mass felt
			+			+		+	Autopsy diagno- sis
o	26,000	+				+	+		Mass felt late
o			+		+			+	
+++	20 000	+		+			+		
o			+	Packed	+		+		
+++	8,500	+		+			+		
+++			+	+			+		
	18,700		+	+			+		
o	11,700	+			+		+		
o			+		+			+	
		+	+	+	+		+	+	
++		+			+		+		

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DISCUSSION—DR RICHARD H MILLER (Boston) This very informative presentation serves to call our attention to a condition which I think can hardly be as rare as Doctor Kilgore has stated I believe cases have occurred more frequently, but they have failed to arouse the interest of the profession enough to lead them to record them in the literature It is extraordinary, when you come to think of it, that only about 20 cases have been noted

The syndrome which Doctors Kilgore and Cushman have noted is indeed worthy of our consideration, and we ought to bear it in mind whenever we are called in to study a doubtful acute abdominal case Their third patient was one in whom they did not definitely prove the diagnosis by operation, and one, on reading the paper, is tempted to say "Well, perhaps it might have been something else" But on further study, one is convinced, from one's own reasoning, that that is what truly obtained, and one can but commend them for making the diagnosis and, once having made it, for adhering to it and carrying out a policy of conservative treatment, when it would have been perfectly justifiable, and easier, to have performed an exploratory operation

When you group all these cases together and study them, it is at once evident that the picture is not entirely a clear-cut one, because several of these patients did not show evidence of any vascular disease, and it is difficult, in view of their comparative youth, to explain the etiologic factors involved I think it is important that such cases, as may be met, be reported and studied more carefully in the future

There are two cases which I will mention, with the greatest brevity The first is one that we had in the Massachusetts General Hospital not long ago, operated upon by Dr Arthur Allen A woman, age 59, with a normal blood pressure, who, following a bad cold accompanied by severe coughing, began to have pain in the left lower quadrant of the abdomen A careful study failed to reveal the exact diagnosis The pain was

characteristic of that of smooth muscle contraction, not of peritonitis. She was finally operated upon, and as soon as the anesthetic was administered, it became obvious that a vague mass, which had previously been felt in the abdomen, was in the abdominal wall, and the lesion proved to be a spontaneous rupture of the deep left epigastric artery, with a large hematoma.

The other case is one which is not positively proved, but is extremely interesting, and I believe to have been an instance of this condition. A man, age 45, with a systolic blood pressure of 250, was operated upon by myself, at his request, for hernia. The operation was uneventful, and there was no trouble until five weeks postoperative, when he was seized with a vague attack of acute abdominal pain, with nausea and vomiting, but no obstruction, no definite tenderness, and no palpable tumor. He continued to have symptoms for seven days, during five of which he passed frequent stools containing blood which was partially changed, neither tarry nor bright red, but of a purple tinge. There was considerable argument as to whether he should be operated upon again, the feeling being that probably he had a very small mesenteric thrombosis.

He recovered without operation. His condition of arteriosclerosis became progressively worse, and at the end of six months he died. Autopsy revealed, about half-way up the ileum, the scar of a recent ulcer surrounded by scar tissue, and it is my belief that he had what was not a mesenteric thrombosis, but a rupture of an artery, with the formation of a small hematoma, interference with the circulation, ulceration of the mucous membrane of the ileum, and hemorrhage.

DR DALLAS R. PHEMISTER (Chicago). I only wish to point out that in hemorrhagic pancreatitis there may be not only an hematoma about the pancreas but an enormous hematoma extending down into the mesentery, producing precisely the clinical picture cited by Doctor Kilgore.

EXPERIMENTAL PRODUCTION OF CHRONIC CHOLECYSTITIS BY OBSTRUCTIVE LESIONS OF THE CYSTIC DUCT*

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It has long been known that complete obstruction of the cystic duct results in definite pathologic changes such as hydrops and empyema, which are associated with a variable degree of inflammation of the wall of the gallbladder and give rise to certain symptoms. It has not been conceded that partial obstruction of the cystic duct would result in definite pathologic changes or symptoms. However, as long ago as 1921, Schmieden and Rhode,¹ and Seelig² called attention to this possibility. Little has been done since then to foster the idea. In 1938, Cole and Rossiter³ called attention again to the possible relationship of obstructive lesions of the cystic duct to inflammation of the gallbladder. This work was instigated by the observation of the high incidence of obstructive lesions in the cystic duct of gallbladders removed in the operating room.

In support of the assumption that partial obstruction of the cystic duct exists and may result in pathologic changes, one might mention the fact that partial obstruction in practically all tubular structures of the body including intestines, ureter, urethra, bronchus, *etc*, almost always leads to symptoms or pathologic lesions, or both. Since the function of the cystic duct is to conduct bile from the common duct to the gallbladder, why should not an obstruction here be fairly common and likewise produce a pathologic condition?

Although various types of obstructive lesions of the cystic duct including anomalous valves of Heister, stenosis, kinking, *etc*, are found, it is somewhat difficult to determine the exact importance of these lesions, chiefly because it is frequently difficult to tell how much obstruction is produced by a given lesion. However, careful examination of the cystic duct of gallbladders removed for cholecystitis will show remarkably few normal ducts, particularly if the duct has been removed close to the common duct.

The incidence of anomalies in this area is well exemplified by the study of Flint,⁴ who noted that in 200 cadavers an anomalous condition of the cystic artery, bile ducts, hepatic artery, and gastroduodenal artery existed in 65 per cent of the cases. In a study of 194 cadavers, Lurje⁵ found an anomalous arrangement of cystic duct alone in 53 per cent of specimens examined. These two studies contain observations only on the anatomic position of the structures, and make no mention of anomalies inside the duct,

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yet it seems likely that a large proportion of the lesions described by them would result in partial obstruction

By producing obstructive lesions of the cystic duct, after methods to be described presently, we obtained changes in the gallbladder identical to chronic cholecystitis in the human, in practically 100 per cent of the cases. These changes, however, were minimal for three or four months, and did not become marked until eight or ten months had passed since production of the obstruction. Although we did not conduct experiments to explain the mechanism of the production of the lesion, certain possibilities seem apparent. We initially tried to produce a lesion which might have a valvular action, thereby allowing bile to enter the cystic duct more readily than get out. We found, however, that the lesion in the fundus was produced regardless of whether or not the obstructive lesion was of such a nature as to produce a valvular action. Concentration of the bile in the gallbladder (seven or eight times under normal circumstances) results in a definite increase in viscosity. Since the lumen of the cystic duct already is relatively small for the transmission of a viscid fluid, the increase in viscosity would obviously exert a rather marked influence in retardation of the exit of the bile into the common duct. It seems logical to us that this chronic partial obstruction would result in an overconcentration of bile, thereby exposing the mucous membrane to a fluid which might be damaging to it.

This theory of chemical cholecystitis is not as yet generally accepted, but is rapidly gaining momentum. It was originated several years ago by Denton⁶ and Feinblatt⁷. One of the features impressing Feinblatt with the fallacy of infection as the primary lesion was the fact that in 20 cases of empyema of the gallbladder he found the contents to consist for the most part of cholesterol and debris, and yielded a positive culture in only 40 per cent of the cases. This idea has been promoted to a greater extent by Andrews and associates⁸. They noted that if bile, concentrated to no more than one-half its volume, were injected into a dog's gallbladder a severe cholecystitis invariably resulted, and concluded that the changes obtained were primarily chemical. These changes have been reproduced by Womack and Bricker,⁹ who concluded that the pathologic lesion resulting from exposure of the gallbladder mucosa to a bile concentrated no more than twice normal, was identical to chronic cholecystitis of human beings. This idea is being accepted by more and more investigators, and is the basic factor behind the fact that cholecystectomy can be performed for acute cholecystitis with only rare development of peritonitis and with a very low mortality rate.

The relatively low incidence of positive cultures of bile and gallbladder wall from gallbladders removed at operation cannot be considered data supporting the infectious etiology of cholecystitis in the human being, at least not in all instances. Judd and associates¹⁰ found a positive culture in the bile in 14 per cent of cases of cholecystitis, and a positive culture in the gallbladder wall in 49 per cent. These figures represent a fair average of the various reports available. In a summary of reports assembled by Walters

and Snell,¹¹ streptococci and *B. coli* were found with about the same frequency. In acute cholecystitis, the percentage of positive cultures will be slightly higher.

Although these experiments were not concerned with the production of gallstones, we found stones in the gallbladder of one animal, and huge deposits of soft tarry material in the gallbladder of another animal, both of which had had a partial obstruction of the cystic duct for about two years. The experimental work of Phemister and associates,¹² showing that the deposition of calcium as stones, or on stones in the gallbladder is dependent upon the degree of obstruction of the cystic duct, supports to a certain extent our theory that partial obstruction will produce pathologic changes. The relationship between complete obstruction of the cystic duct (by stone) and cholecystitis has been discussed adequately by these authors and need not be cited here.

The most obvious explanation of production of chronic cholecystitis by chronic obstruction of the cystic duct as noted in our experiments, would appear to lie in the production of a chemical cholecystitis (similar to that described above) followed later by a superimposed infection in many cases. This hypothesis does not conflict with the method of infection by lymphatic channels as brought out by Graham¹³ many years ago. In fact, it is our assumption that in our animals, the infection, as found in 30 per cent of chronically inflamed gallbladders, took place by such a mechanism. That principle is, therefore, needed to explain part of the findings in our work.

Methods of Experimentation—Three different methods of producing a partial obstruction of the cystic duct were utilized. (1) A small flap of gallbladder wall was outlined in the neck of the gallbladder (Fig. 1), the flap turned into the lumen of the organ and the opening closed. We thought this flap might remain as a mobile piece of gallbladder wall obstructing the cystic duct because of its position directly over the opening. However, we discovered that as the lesion healed the flap became rounded and developed into a pear-shaped nodule (Fig. 1). If the flap were made in the proper position at the junction of the neck of the gallbladder and opening of the cystic duct, it would protrude against the opposite wall of the neck of the gallbladder producing an obvious partial obstruction of the valvular type because of its position on the gallbladder side of the cystic duct. After two or three trials we found it was not difficult to place this flap at the proper position. Control flaps were made in the dome of several dogs to eliminate the possibility that simple incision through the gallbladder wall might produce a lesion which would spread throughout the entire gallbladder. We noted a definite thickening of the gallbladder wall surrounding the site of the control flap in the dome, but in no instance did this fibrous tissue extend further than 1 or 1.5 cm. beyond the operative site.*

* Attention is called to the universal temporary diffuse reaction consisting primarily of edema in the wall following even trivial injuries of the gallbladder wall, however, this injury in our experience heals without residue if inflicted in the dome of the gallbladder.

(2) Partial obstruction of the cystic duct was also produced by taking three or four interrupted mattress sutures of silk in the neck of the gallbladder at the margin of the cystic duct, thereby infolding the wall against the opposite side. This procedure amounts to taking a tuck in the wall, and produced a partial obstruction in three of the four animals upon which the procedure was performed.

(3) The cystic duct was crushed in seven animals, thinking that when healing took place a stenosis would result. In spite of the fact that the crushing was thought to have been thorough we noted, to our amazement, that the injury healed in about half of the animals without any obvious residual lesion. This method was, therefore, considered unreliable, at least in our hands, for the production of an obstruction. Perhaps the crushing was not sufficiently complete.

Results of Experiments—All together, 36 animals were used. Two of these died a few days postoperatively, and two represent errors in technic, insofar as our attempt to produce a partial obstruction actually resulted in a total obstruction. These animals with total obstruction of the cystic duct showed a small shriveled gallbladder, as observed at a later date, containing no bile, but naturally showed evidence of inflammation. These four animals, therefore, had to be discarded.

Of the remaining 32 animals, nine had the operation consisting of production of a flap in the neck of the gallbladder at the junction with the cystic duct. These dogs were sacrificed at various intervals ranging from two to 24 months following the operation (Table I). One animal was sacrificed at two months, and practically all the remaining had operations at three months (but were not killed) to observe any gross changes present. None of the animals in any series showed any gross change (except edema) at operation or at autopsy, when the obstruction was produced less than four months previously. On several occasions, when observations were obtained a few days or a few weeks following operation, edema was noted, regardless of the type of operation, as previously discussed. Of the nine animals having flaps produced at the neck of the gallbladder, one was sacrificed at two months, too early for development of change, and thereby actually served as a control. Table I reveals that of the remaining eight, all except one

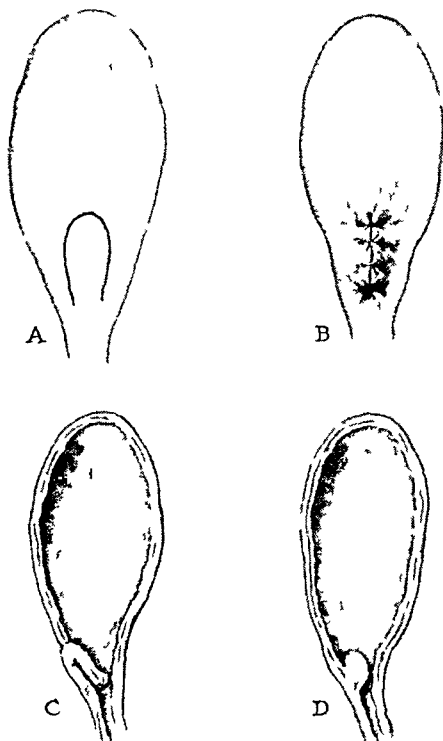


FIG. 1—The most effective of the three methods tried for production of partial obstruction of the cystic duct. A A flap is outlined in the neck of the gallbladder, and is turned in with closure of the defect as shown in B and C. Usually the flap becomes rounded as depicted in D, but frequently disappears leaving a densely scarred area with obstruction at the proximal opening of the duct.

TABLE I

	Dog No	Dur Obst Mo	Gross Change	Culture	Thickness (Times Normal)	Obst Prod in Cyst Duct	Remarks
Flap at neck of G B	1	24	++++	An strep	5 5 X	Yes	
	2	24	+++	Neg	4 5 X	Yes	Stone at cystic duct
	3	19	+++	Staph & strep	4 X	Yes	
	4	15	o to +	Neg	-2 X	No	No evidence flap or oper
	5	8	++		2 X	Yes	
	6	7	++	An strep	4 X	Yes	Flap gone, stricture
	7	7	+++	Neg	3 X	Yes	
	8	6	++	Neg	2 8 X	Yes	Soft stones?
	9	2	+		1 5 X	Yes	Too early for change
Tuck at neck of G B	10	12	+++	Neg	5 X	Yes	
	11	11	+	Neg	2 X	?	
	12	7	+++		3 X	Yes	
	13	4	+	Neg	2 X	?	Insuf time
Crush cystic duct	14	17	++++	Neg	4 X	Yes	Stricture
	15	15	o	Neg	1 4 X	No	
	16	12	o	Contam ²	1 0 X	No	
	17	7	+++	Neg	2 5 X	Yes	Stricture cholesterosis
	18	7	+++	Neg	3 5 X	Yes	Stricture
	19	7	o	Neg	1 X	No	
	20	o 3	+(Edema)		2 X	?	Too early for change
Ligate cystic artery (No obst)	21	19	o		1 X	No	
	22	16	o	Neg	1 X	No	
	23	8	o	Neg	1 X	No	
	24	7	o		1 X	No	
	25	5	o		1 X	No	
	26	4	o		1 X	No	
Control Flap midway	27	11	o to +	Neg	1 5 X	No	
Control Flap in dome	28	11	o	Neg	1 X	No	
	29	9	o		1 X	No	
	30	9	o		1 X	No	
	31	8	o	Neg	1 X	No	
	32	4	o	Neg	1 X	No	

Note that chronic cholecystitis was produced only in the animals in which an obstruction of the cystic duct was produced. chronic cholecystitis was produced in every gallbladder when the cystic duct was obstructed. The procedure of turning in a flap of gallbladder wall at the neck of the gallbladder was the most effective.

showed marked change of the type similar or identical to chronic cholecystitis as seen in human beings. The maximum thickness of the gallbladder, as measured microscopically on the sections, was 5 5 times normal. The average thickness of the eight gallbladders was slightly less than three and one-half times normal. It should be stated that the sections removed for microscopic study were removed from the fundus, as far as possible from the operative site. At postmortem, the gallbladder, in all instances except one (when no obstruction was produced), had lost its bluish color, presented a grayish-black-red color, and had an obvious thickening of the wall. There were numerous adhesions of the omentum to the gallbladder in almost all cases. One of the eight gallbladders contained definite, firm stones. An additional one contained thick desiccated bile which was lumpy, indicating that stone formation was beginning. This animal had had an obstruction produced only

six months previously, suggesting that an additional length of time might have shown more definite stone formation

The microscopic change consisted primarily of fibrosis affecting the wall of the gallbladder. This fibrosis was located primarily in the muscularis and in the areolar tissue between the muscularis and serosa. Edema was found on numerous occasions regardless of the length of time since production of the obstruction. There was an infiltration of lymphocytes in all gallbladders showing significant change. This infiltration was diffuse but most marked in the submucosa. On numerous occasions the mucosa was gone. Realizing that the gallbladder mucosa can readily be lost during the process of fixation and staining, not a great deal of importance can be attached to this feature. However, it is significant that there was no loss of mucosa in any of the gallbladders showing no gross pathologic change. It is noted, therefore,

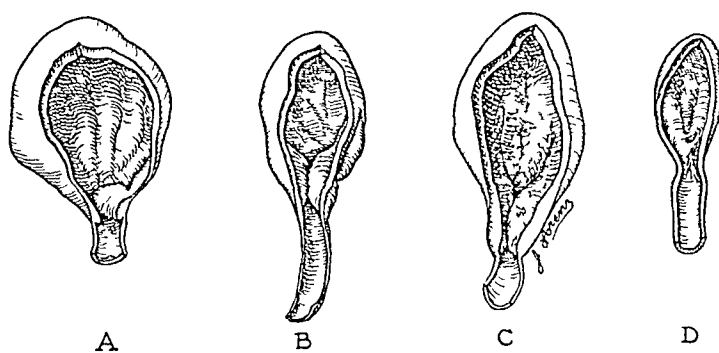


FIG 4.—Drawings of four types of obstructive lesions produced in the cystic duct. A and B Produced by turning in a flap at the junction of the cystic duct and neck of the gallbladder, 7 and 19 months previously, respectively. C Produced by infolding the wall of the gallbladder just above the cystic duct, 12 months previously. D Produced by crushing the neck of the gallbladder and cystic duct, 17 months previously.

that seven of the eight gallbladders in this series showed very definite and pronounced evidence of chronic cholecystitis. The case showing no cholecystitis (Dog No. 4) revealed no evidence of obstruction at the junction of the cystic duct where the operation had supposedly been performed, neither was there any stenosis. In view of the fact that we could not find any changes at the operative site, the question was even raised as to whether or not there was an error in numbering the animals. We, however, classified this as an operative failure, but it does not influence the incidence of chronic cholecystitis in animals with partial obstruction of the cystic duct produced by this method, since all seven animals with obstruction of the duct showed a definite and fairly severe grade of chronic cholecystitis.

In four animals, an obstruction was produced at the junction of the cystic duct and neck of the gallbladder by taking a tuck at that point. This tuck, which was produced by mattress sutures, obviously resulted in an infolding of the wall into the lumen just above the cystic duct. Of these four animals (Table I), only two demonstrated definite pathologic changes. The other two showed only very slight pathologic change, examination of

the duct revealed that only a very slight ridge or infolding of tissue remained. One of these animals was sacrificed at the end of four months, but in view of the mild or doubtful obstruction produced, we would not expect much increase in the pathologic change even though many more months had elapsed.

In seven animals, the cystic duct was crushed at several areas with an artery forcep. Examination of the cystic duct revealed the fact that in only three animals was a stenosis produced by the crushing, in only these three was a definite cholecystitis produced. One of these gallbladders was the seat of a marked cholesterosis. One of the remaining four animals (Dog No. 20) was killed in a fight on his ninth postoperative day. As expected, the gallbladder wall showed edema and was moderately thickened, but the animal must be discarded because of inadequate time-interval since operation. In other words, this procedure resulted in positive results in only one-half of the cases, primarily because with the type of crushing performed we were unable to produce a stenosis or obstruction of any type, in half the cases.

In six animals, the cystic artery along with adjacent lymphatic ducts was ligated, to determine whether or not obstruction of the blood supply with adjacent lymph vessels would produce cholecystitis. In none of the six animals was there the slightest change noted in the gallbladder wall. The time interval since operation varied from four to 19 months (Table I). It should be stated, however, that this procedure will result in production of a significant edema several days after operation, but this edema disappears in several days or a few weeks leaving a normal gallbladder wall.

One animal (Dog No. 27) had a flap turned in at the junction of the middle and lower third of the gallbladder. This animal really serves as a control since no obstruction was produced. No changes other than those which might be secondary to a celiotomy were noted in this animal.

In five animals, control flaps were made in the dome of the gallbladder. The time-interval since operation varied from four to 11 months. In no instance was there any gross change or thickness of the gallbladder wall, except at the exact site of the operation, as noted at microscopic examination. These animals serve as controls, particularly for the ones having a flap turned in at the neck of the gallbladder.

Cultures were taken on the gallbladders of 22 animals. In ten of these animals, a definite obstruction had been produced with resultant pathologic changes in the gallbladder wall identical to chronic cholecystitis in the human being. The culture was positive in three instances, resulting in positive cultures in 30 per cent of the cases showing cholecystitis. All three of these positive cultures were obtained in the animals having had an obstruction produced by turning in a flap just above the cystic duct, thereby supporting the information already obtained that obstruction produced by a flap at the cystic duct was the most effective of the three methods tried. In two instances (Dogs Nos. 1 and 5) anaerobic streptococci were isolated from the gallbladder wall and bile. In one of these it was an *alpha* hemolytic streptococcus and in the other a *beta* hemolytic streptococcus. In Dog No. 3 a

Staphylococcus albus and an *alpha* streptococcus were isolated from the gallbladder wall and the bile. The staphylococcus was present as a heavy growth (12,000 per cc of bile), and the streptococcus almost as heavy

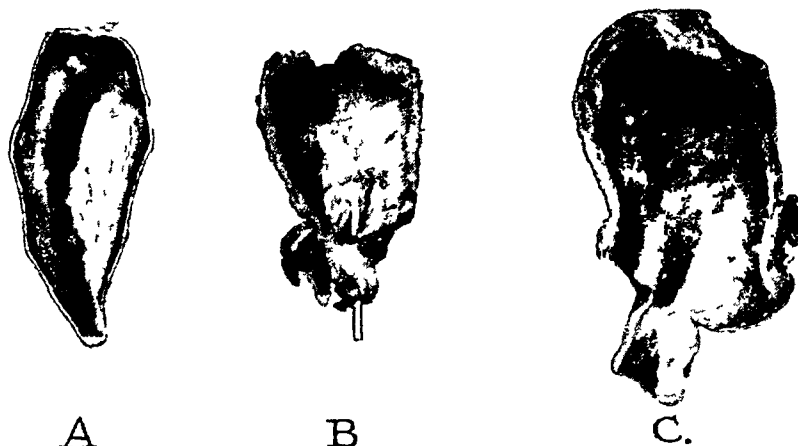


FIG 3—Photograph of three gallbladders. A Control Flap made in dome 11 months previously. No gross or microscopic change noted except at the operative site (Fig 4). B Partial obstruction of cystic duct produced by inversion of a flap at the neck of the gallbladder 24 months previously. The small probe in the cystic duct reveals how the irregularly shaped nodule at the site of the flap compresses the opening of the duct. Note thickness of gallbladder wall as compared to the control. C Partial obstruction produced by flap turned in at the neck of the gallbladder, 24 months previously. The flap disappeared, but a diffuse scar with severe contraction and consequent obstruction remained. Note the thickening of the gallbladder wall, a photomicrograph of which is shown in Figure 6.

(10,800 per cc of bile). On one other occasion (Dog No 16) a few staphylococci were found, but were considered to be contamination. This incidence of 30 per cent positive cultures in the bile and wall of the gallbladders in which chronic cholecystitis was produced, compares favorably with the incidence of positive cultures in chronic cholecystitis in the human being. It seems particularly significant that in all gallbladders without obstruction in which cultures were taken (12 in number), all were negative. Of these 12, five were controls.

COMMENT—It is well known that operative procedures on the gallbladder, even though of minimal degree, result in subacute cholecystitis in a remarkably high percentage of cases. Edema is the important pathologic manifestation of this process. However, this temporary inflammation apparently disappears in several days or a few weeks. We encountered it in some of our cases a few days following operation, but when the animal was sacrificed months later no evidence of cholecystitis remained except when obstruction incident to our operative procedures existed. We resorted to three methods of producing obstruction at the cystic duct: (1) Flap in the neck of the gallbladder overlying the entrance to the cystic duct, (2) infolding of the neck of the gallbladder (tuck), (3) crushing of the cystic duct with the hope that a stenosis would be produced. In every gallbladder, in which

a definite obstruction of the cystic duct was produced (12 in number), a pronounced cholecystitis with thickening of the wall by fibrosis, and lymphocytic infiltration was observed. Of the three methods utilized for producing an obstruction of the cystic duct, the first one named (flap at neck) was the



FIG 4—Low power photomicrograph of control gallbladder (same as Fig 3A) in which a flap was turned in on the dome 11 months previously. No obstruction was produced at the cystic duct. There are no pathologic microscopic changes (X65)



FIG 5—Low power photomicrograph of dome of gallbladder in which a flap was turned in at the neck 24 months previously producing a partial obstruction of the cystic duct. According to measurements made on the slides microscopically the wall was five and one half times thicker than the control illustrated in Figure 4. A dense deposition of fibrous tissue may be noted in the submucosa and muscularis. The tissue external to this represents edematous granulation tissue in various stages of resolution. Lymphocytic infiltration is diffuse but polymorphonuclear cells are uncommon (X65)

most effective, failing to produce an obstruction in only one instance (88 per cent successful). The second and third methods just described were successful in producing obstruction in 50 and 43 per cent, respectively. As stated, without exception the failures in production of cholecystitis occurred in the gallbladders in which the operative procedure failed to produce an obstruction at the opening of the cystic duct.

CHRONIC CHOLECYSTITIS

To prove that disturbance of the blood supply, as would result from our operative procedures at the neck of the gallbladder, was not responsible for the cholecystitis, we ligated the cystic artery and adjacent lymphatic ducts in six animals. Although a temporary edema with gross thickening of the wall of the gallbladder results from such a procedure, complete recovery takes

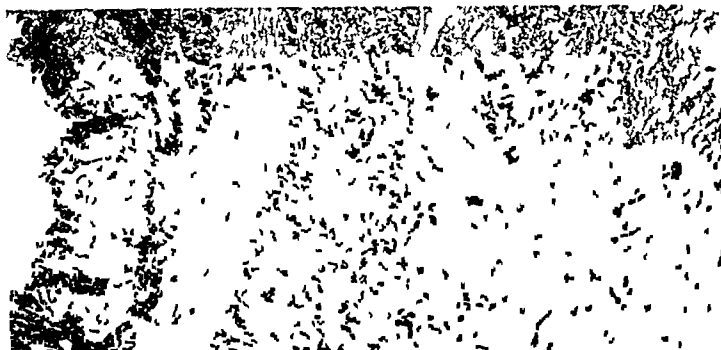


FIG 6—Low power photomicrograph of dome of gallbladder. A flap was turned in at the junction of the cystic duct and neck of the gallbladder, 24 months previously, resulting in a stenosis of the cystic duct (same gallbladder as in Fig 3C). Chronic cholecystitis was produced. The wall is four and one half times as thick as the control shown in Figure 4. The microscopic changes are the same as in Figure 5, however, two stones were found in the gallbladder lumen ($\times 65$)



FIG 7—Moderately high power of gallbladder wall shown in Figure 6. The field depicted is between the muscularis and submucosa. Note the area of lymphocytic infiltration (L) near the mucosa, and the dense connective tissue (C) deeper in the wall. The microscopic picture is identical to that seen in a severe grade of chronic cholecystitis in the human being.

place, when these animals were sacrificed at intervals of four to 19 months following operation (Table I), not a single one exhibited evidence of cholecystitis. Moreover, control flaps were made in the dome of the gallbladder in five animals. In none of these was there evidence of cholecystitis at the time they were sacrificed, between four and 11 months following operation. It is obvious, then, that production of an obstruction at the neck of the gallbladder at the entrance of the cystic duct is the primary factor in the produc-

tion of the cholecystitis obtained. As noted in Figure 1, the flap changes markedly in shape, it usually becomes pear-shaped and consists entirely of a fibrous nodule, which projects inward over the opening of the cystic duct. Such a lesion would appear to interfere more with emptying of the organ than with its filling. The degree of cholecystitis produced was only slightly more pronounced than in gallbladders in which obstruction to the duct had been produced by other means.

As previously intimated, it is our assumption that this chronic inflammation is produced by exposure of the gallbladder mucosa to bile which is overly concentrated because of the chronic obstruction at the cystic duct. Attention has already been called to the fact that injection of gallbladder bile concentrated to twice normal (Andrews, Womack, and Bicker) will produce an acute cholecystitis, sometimes gangrenous in type. Presumably, the concentration in a partially obstructed gallbladder does not approach twice normal concentration, otherwise, we would have encountered acute cholecystitis perhaps with gangrene. It would appear that exposure of the gallbladder lumen over a period of months, to a bile concentrated slightly beyond normal might result in a chronic inflammation.

The incidence of positive cultures in the gallbladders with partial obstruction of the cystic duct showing cholecystic changes was 30 per cent. This corresponds closely with the incidence of positive cultures obtained in the wall of infected gallbladders of human beings. It is our contention that the organisms found in these specimens represented a secondary infection implanted on a chemical cholecystitis.

TABLE II

LESIONS WHICH MAY BE RESPONSIBLE FOR PARTIAL OBSTRUCTION
OF THE CYSTIC DUCT*

- (1) Congenital or inflammatory lesions involving valves of Heister
 - (a) Valve like anomalies
 - (b) Fibrous strands
 - (c) Local deposition (nodules) of fibrous tissue
 - (d) Stricture due to scar
- (2) Congenital or inflammatory twists or kinks
- (3) Stenosis produced by a thickened wall
 - (a) Due to acute inflammation
 - (b) Due to diffuse fibrosis
- (4) Stenosis produced by surrounding adhesions
- (5) Stone in the duct
- (6) Tension induced by enlarged liver
- (7) Compression or filling defect due to tumor or lymph nodes
- (8) Obstruction due to anomalous hepatic or cystic artery

* The authors are of the opinion that the first four types of obstruction would be the most important (from the standpoint of frequency) in the production of chronic cholecystitis by the mechanism herein suggested.

We do not infer that this mechanism of production of cholecystitis by partial obstruction of the cystic duct takes place in every instance of cholecystitis. However, the ease with which it is produced in animals, and the frequency of anomalous obstructive lesions in the cystic duct of gallbladders removed at operation, lead us to believe that it is a very frequent mechanism.

in the production of chronic cholecystitis. In a study of incidence of obstructive lesions of the cystic duct in humans (not yet published) Jensik¹⁴ has found them much more frequent in diseased gallbladders removed at operation than in normal gallbladders as removed at autopsy.

As previously stated, this hypothesis does not contradict the infective theory of lymphatic transmission as suggested by Graham many years ago. In fact, the infective theory is necessary to explain part of the findings in our experiments, insofar as the infection (positive culture) found in 30 per cent of the gallbladders with cholecystitis, in our experiments, was most likely explained by transmission from the liver through the lymphatics.

The fact that obstruction of the common duct by a lesion such as carcinoma of the pancreas does not give rise to cholecystitis, would at first appear to contradict the theory of origin of cholecystitis from partial obstruction of the cystic duct, as herein discussed. However, this apparent discrepancy can be explained readily. It has long been known and proved that almost immediately after an obstruction of the common duct is produced, the excretion of bile salts by the liver decreases to very low values. In that case, there would not be sufficient bile salts in the biliary tree to result in over-concentration in the gallbladder, chemical damage to the gallbladder wall from that source would, therefore, be impossible. The fact that obstruction of the common duct by lesions such as carcinoma of the pancreas does not instigate the development of cholecystitis, in reality, then supports the theory of origin from partial obstruction of the cystic duct.

Another peculiar feature of gallbladder disease, which might appear to be inconsistent with the theory herein presented, is the fact that cholecystitis is, in reality, a disease of adults. The question might be asked—if partial obstruction of the cystic duct such as produced by kinks, anomalous valves, *etc.*, are important in the pathogenesis of cholecystitis, why should the disease not be more common in childhood, since many of the obstructive lesions mentioned are congenital in origin? This question might be answered in many ways. In the first place, there are innumerable diseases which are much more common in late adult life than in childhood, when the etiologic factors *presumably* exist to the same extent in childhood as in late adult life. Among these may be mentioned cholelithiasis, arteriosclerosis, hepatic cirrhosis, carcinoma, and many others. The truth is that there, obviously, are reasons (chiefly physiologic) in all instances for the variation in incidence of cholecystitis in the various age-groups. An important reason for the infrequency of chronic cholecystitis in childhood may be contained in the possibility that there may be sufficient differences in the ratio of one bile salt to another in children, *versus* that in adults, to account for a different chemical action. After all, bile salts may not be the all-important factor in the production of chemical cholecystitis, the toxic action may be due to an allied salt, minute in quantity, which is not present normally until late in life. Perhaps the mucosa of the gallbladder in children is more resistant to injury or more impermeable to bile salts.

Another explanation may lie in the fact that although many lesions exist at birth they do not become obstructive to a damaging degree until they are actually increased in mass by the numerous assaults, from the wear and tear of time, which might gradually increase the amount of fibrous tissue and, therefore, the size. Anatomically, the tissue about the common duct and terminal end of the cystic duct contains many lymphatic channels communicating between the liver and celiac lymph nodes, and, perhaps, some draining directly from the intestine. It is well known that the liver is at all times being exposed to organisms brought to it from the intestinal tract by the portal vein. At frequent intervals, during attacks of hepatitis of bacterial origin some organisms no doubt spill over into the lymph ducts. It seems possible that the resultant lymphangitis would result in scar formation sufficient in some instances to produce partial obstruction of the cystic duct, but only after repeated episodes made possible by many years of life. It is, of course, well known that in general, chronic cholecystitis is insidious and very slow in development (shown also in our experiments). This fact in itself is important in explaining the infrequency of chronic cholecystitis in childhood.

SUMMARY

Three different mechanisms of producing partial obstruction of the cystic duct have been devised: (1) Turning in a flap of gallbladder wall at the neck of the organ, (2) infolding of the wall at the neck by mattress sutures (tuck), and (3) crushing of the cystic duct. In every instance when a definite obstruction at the cystic duct was produced, a severe grade of chronic cholecystitis consisting of fibrosis, lymphocytic infiltration, *etc.*, similar or identical to that seen in human beings, was produced. However, the development is so slow that even minimum changes are not demonstrable until four to six months have elapsed since production of the lesion. Maximum effects are not noted until at least two years have elapsed since production of the obstruction. Gallstones were produced on two occasions.

No experiments were undertaken to demonstrate the mechanism of production of the cholecystitis, but it is assumed that the obstruction results in an overconcentration of bile salts and other chemical constituents of the bile, which, in turn, exert a damaging effect on the mucosa of the gallbladder through toxic chemical action. Infection appears to be a late event, and, presumably, is secondarily imposed upon the damaged gallbladder wall. In only 30 per cent of cases of experimentally produced cholecystitis was culture of the gallbladder wall and bile positive.

The first method mentioned, *i.e.*, turning in a flap of the neck of the gallbladder just above the opening of the cystic duct was by far the most effective technic in producing a partial obstruction—failing in only one instance. Controls consisting of infolding of a flap of gallbladder wall in the dome of the gallbladder, and ligation of the cystic artery, with accompanying lym-

phatics, did not result in pathologic changes in the wall beyond temporary edema (except at the immediate site of operation) in a single instance

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DISCUSSION—DR DALLAS B PHEMISTER (Chicago, Ill) Doctor Cole has brought out the fact that there are many cases of gallbladder disease in which there is obstruction of the cystic duct, which are not due to a stone impacted in the duct Now, the degree of obstruction in these cases is extremely variable It may be slight, or it may be so extreme that no bile enters the gallbladder In fact, every so often we encounter a mucocele of the appendage, in which there is no stone either in the gallbladder or in the cystic duct

An illustration shows a patient who had mild symptoms for about nine months, and cholecystography showed nonvisualization of the gallbladder When the gallbladder was removed and cut open, thick mucus welled out There were only a few flecks of pigment in it, and no sign of a stone There was a chronic cholecystitis and also a chronic inflammation of the excised stump of cystic duct of somewhat comparable degree

This cystic duct obstruction from noncalculus processes may cause a variation in the cholesterol, calcium and pigment contents of stones that form in the gallbladder, and, in general, the greater the degree of obstruction, the greater the likelihood that the stones will contain calcium and pigment, also, when the obstruction is of a high degree there may be free calcium in the gallbladder, as in the case illustrated by these lantern slides The gallbladder was the seat of a mucocele, and, in addition, contained cholesterol-pigment stones and roentgenogram of an excised gallbladder in which there was no separate particles casting the heavy shadows of calcium carbonate The cystic duct was the seat of a chronic obstructive cholangitis and free from stone

Now, I have assumed the pathogenesis of these cases to be either a chronic cholecystitis, with extension of the infection to the cystic duct, or damage of the duct by passage through it of stones from the gallbladder. However, it is quite possible that Doctor Cole's explanation is correct, and that, in some cases, there are other factors that are responsible for duct obstruction.

DR NATHAN A. WOMACK (St. Louis, Mo.) For a long time, the association between complete obstruction of the cystic duct and acute cholecystitis has been recognized. Doctor Cole and his colleagues have now shown definitely the relationship between partial cystic duct occlusion and chronic cholecystitis. One cannot easily find fault with either the experimental or clinical evidence that they have presented. The question that must be answered, however, is why does the obstruction produce the inflammation. Ordinarily obstruction produces distention. Obstruction produces inflammation only when the substance obstructed is injurious to tissue.

Recently, in a preliminary report, Bricker and I presented evidence to show that this injurious substance was bile. In the experimental animal, if the gallbladder is washed free of bile and filled with physiologic salt solution, complete obstruction of the cystic duct results in mucocele. If the cystic duct is ligated without disturbing the bile in the gallbladder, a moderate degree of acute inflammatory change appears, which subsides. If, however, concentrated bile is placed in the gallbladder, severe inflammatory change is produced, and this seems to be almost in direct proportion to the concentration of the bile. Where half of the water is removed, gangrene of the gallbladder occurs in many instances. Various components of bile were studied, namely, cholesterol sodium deoxycholate, and sodium glycocholate and a solution of commercial dried bile, with comparable results. Inflammatory changes noted were identical to those seen in human cholecystitis, and were also similar to the cellular reaction seen when these substances are injected subcutaneously in the experimental animal.

We feel, therefore, that the etiology of cholecystitis is concerned with obstruction and imprisonment of bile, which becomes concentrated and, in turn, damages the gallbladder and perhaps liver tissue, leaving it susceptible to secondary bacterial invasion.

DR W. H. COLE (Chicago, Ill., closing) I have merely one point to add, namely, to emphasize the fact that in these experiments we are dealing only with partial obstruction of the cystic duct. The relationship of complete obstruction of the cystic duct to gallbladder disease is well known. In three or four animals we made a technical error and produced a complete obstruction of the cystic duct instead of a partial one, these animals were discarded.

CEREBROSPINAL RHINORRHEA SURGICAL REPAIR OF CRANIOSINUS FISTULA*

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THE FAILURE of a cramosinus fistula with leakage of cerebrospinal fluid to close after the accepted procedure of suturing the rent in the dura, through a unilateral frontal craniotomy, prompted me to develop an operation which would effect permanent closure and cessation of the rhinorrhea.

This report includes a review of three cases in which the patients were successfully treated by the present method†. In the first case, cerebrospinal rhinorrhea occurred in a boy ten years of age, who had sustained a fracture of the skull involving both walls of the frontal sinus. Rhinorrhea had been present for eight and one-half years. In the second case, the patient was a man age 43, in whom rhinorrhea developed as the result of a fracture of the skull which extended into the cribriform plate of the ethmoid bone. The force producing the fracture came from a 50-lb. weight which was dropped on the vertex of the skull, producing a depressed fracture at the point of contact as well as a fracture involving the ethmoid. Although bloody discharge from his nose occurred at the time of injury, drainage of cerebrospinal fluid did not occur until six months later, at which time he appeared to have a head cold. Rhinorrhea continued for six months and endured until the time of his operation. In the third case, the patient was a woman, age 34, in whom spontaneous cerebrospinal rhinorrhea developed and was present for nine and one-half months. The cerebrospinal fistula in this case consisted of a communication between the meninges through the ethmoid into the nasal cavity. Craniotomy revealed an opening in the cribriform plate through which an olfactory nerve fiber descended, the opening was much larger than normal, being 2 Mm. in diameter. A villus of arachnoid extended through this opening into the ethmoid where apparently, it had given away, accounting for the leak of cerebrospinal fluid. Normal relationships of the brain, meninges, and anterior portion of the skull are shown in Figure 1a.

Causation—Cerebrospinal rhinorrhea may result from a number of causes, the most common of which is skull fracture that extends through the posterior wall of the frontal sinus (Fig. 1b) or the cribriform plate of the ethmoid bone, with accompanying tears of the dura and arachnoid^{1, 7}. The first evidence of rhinorrhea associated with fracture of the skull is the occurrence of a watery, bloody discharge from the nose. In most instances, in my experience, the lesions heal with spontaneous remission of the rhinorrhea. Persistent rhinor-

* Read by title before the meeting of the American Surgical Association, White Sulphur Springs, W. Va., April 28-30, 1941.

† Three additional cases have been operated with equally as good results.

rhea or the delayed occurrence of rhinorrhea usually is due to considerable loss of bone, absorption of a fragment of bone, or inclusion of the dura and arachnoid between fragments of bone which permits escape of cerebrospinal fluid into one of the nasal cavities. Cerebrospinal rhinorrhea frequently has occurred spontaneously, just as it occurred in my third case, and when it does occur, it probably is the result of a congenital defect in the cribriform plate which permits extension of an envelope of arachnoid along an olfactory nerve fiber through the cribriform plate. Leakage of cerebrospinal fluid undoubtedly is the result of rupture of the thinned-out arachnoid and mucous membrane. According to reviews in literature, precipitation of this type of rhinorrhea usually is the result of coughing or sneezing during an attack of head cold. Rhinorrhea has accompanied hydrocephalus, and in that particular instance leakage of cerebrospinal fluid was the result of increased intracranial pressure on thinned-out membranes and absorptive defects of the cribriform plate. I have also seen the condition afflict two patients suffering from pituitary tumor. The floor of the sella turcica had been absorbed, with presumable leakage of cerebrospinal fluid into the sphenoidal sinus. I also saw the condition in a patient who had a large osteoma of the orbit which had extended through the ethmoid into the anterior fossa. Rhinorrhea also has followed the removal of nasal polyps. The polyps probably were meningoceles that had extended through the cribriform plate. Rhinorrhea also has resulted from craniotomy when, in the making of the anterior margin of the bone flap, the frontal sinus was unintentionally opened.

Symptoms and Signs—The only symptom that many patients complain of is an annoying, watery discharge of the nose. It may be continuous or cease for only a few hours before it continues. The discharge may appear as drops of clear fluid or it may pour out in a stream when the head is tilted in certain positions. Usually, it appears in one side of the nose and produces the sensation that is experienced when the nose is congested. In acute injuries of the head, it may be difficult to recognize cerebrospinal fluid because it is mixed with blood, but when the condition is chronic the fluid is watery and can be readily collected and examined chemically. Cerebrospinal fluid is colorless, limpid, slightly viscous, has a specific gravity of 1.004 to 1.008, and contains traces of protein and small quantities of inorganic salt and dextrose. The lymphocyte count varies from five to ten cells per cubic centimeter of fluid. If there is doubt about the presence of cerebrospinal fluid in a discharge from the nose, the indigo carmine test in which 1 cc. of indigo carmine is introduced into the subarachnoid space of the spinal canal by means of routine spinal puncture might be employed. Since the dye promptly stains the cerebrospinal fluid a bluish-green color will be seen to appear in the nasal discharge within about 15 minutes and will continue for two or three hours, if fluid discharging from the nose contains cerebrospinal fluid. This test is of particular value in the differentiation between cerebrospinal rhinorrhea and allergic and vascular rhinorrhea. Roentgenologic examination of the skull offers some aid in the diagnosis in cases of recent fracture, but rarely is such examination of much

assistance in the localization of cerebrospinal fistula involving the ethmoid cell

Meningitis is the serious complication which may accompany this condition. It occurs more often when rhinorrhea results from fracture of the skull than it does when rhinorrhea occurs spontaneously, but it is a constant threat in all cases, and especially so when the patient has contracted a nasopharyngeal infection. Fortunately, chemotherapy has proved of value in combating meningitis and also has made it possible to perform these extensive operations without fear of the development of meningitis.

Conservative Treatment—Conservative treatment (nonoperative) often has been employed by those who feared to advise or employ the radical procedure designed to close the fistulous tract. The argument set forth by those who advocate conservative treatment is that they believe it safer not to disturb the patient than it would be to hazard a radical operation. Unfortunately, there is little to offer in the way of nonoperative treatment. Fox,⁵ and Friedberg and Galloway⁶ reported two cases in which spontaneous cerebrospinal rhinorrhea was controlled by the application of a 20 per cent solution of silver nitrate. Fox identified the opening through the cribriform plate by the use of indigo carmine, after which he applied the solution of silver nitrate several times, with apparent recovery of the patient. Friedberg and Galloway stated that they observed the cerebrospinal fluid entering the nasal cavity at a point at which the anterior third portion of the middle turbinated bone joins the middle third portion of this turbinate, at which point they applied a 20 per cent solution of silver nitrate. The discharge ceased within 12 days and the patient had been free of rhinorrhea for 14 months, at the time of the report. Conservative treatment is of definite value in cases of acute rhinorrhea accompanying fracture of the skull, since a number of the meningeal defects will heal spontaneously. Teachenor,¹⁰ Dandy,⁴ Cairns,² Munro,⁸ and Coleman³ have advocated surgical repair of the meninges, if rhinorrhea does not disappear within four to six days after the time of injury. The approach employed is a transfrontal sinus approach, in which the dura is exposed at the point of injury. Teachenor has suggested removal of the posterior wall of the frontal sinus, along with craniotomy. Lesions involving the ethmoid and the overlying meninges have been dealt with more conservatively than this in cases in which the condition is acute. However, Coleman has employed unilateral frontal craniotomy in repair of recently injured meninges over the ethmoid bone. It has been my experience that if spontaneous recovery from cerebrospinal rhinorrhea is to take place after fracture of the skull, it may not do so for an interval extending from a few days to eight weeks, and, therefore, it has been my practice to limit the intake of fluid to 1500 cc per day, in order to decrease the output of cerebrospinal fluid, and to administer sulfanilamide or sulfathiazole in doses of 60 to 90 gr (4 to 6 Gm) per day, until the concentration of sulfanilamide in the blood registers from 8 to 12 mg per 100 cc. Also, I have found it advantageous to have the patient remain in bed in a semierect posture, making sure that the patient sleeps in the same position, since this minimizes the flow of cerebrospinal fluid into the nose. In the event that

conservative measures fail to effect spontaneous remission of the rhinorrhea, I should advise the procedure employed in the treatment of the three patients to be mentioned herein

Surgical Treatment—Although fractures of the skull are common, a relatively small group develop cerebrospinal rhinorrhea. Coleman reviewed '940 cases of head trauma observed at the Neurosurgical Service, Hospital Division, Medical College of Virginia, in 1935-1936, there were 216 fractures of the skull, with 87 fractures of the base. Of the 87 basal fractures, 15 involved the frontal sinuses, six of these were associated with severe, compound, depressed fractures of the frontal vault, and operation was promptly performed for disinfection, debridement and closure of the dura." His observations are similar to those of others. The incidence of rhinorrhea after fracture of the skull varies from 2 to 5 per cent. In view of the fact that rhinorrhea sometimes is spontaneously cured, I am inclined to wait six or eight weeks before advocating repair of the cranosinus fistula unless the fracture is compound and involves both walls of the frontal sinus.

The accepted procedures for closure of cranosinus fistulae which communicate with the frontal sinus, ethmoid cells, and the nasal cavity have been (1) In cases in which the condition is acute, surgical repair through the frontal sinus, (2) in cases in which the condition is chronic when it is possible to identify the site of the lesion, performance of small unilateral transfrontal craniotomy, identification of the fistula, and closure of the meningeal opening with interrupted silk sutures or closure of it with sutures and covering of it with muscle, and (3) performance of unilateral transfrontal craniotomy, in which the dura is elevated, the opening is identified and a wick of iodoform gauze is placed between the lacerated dura and the cribriform plate, as Peet has advocated. The end of the gauze wick is brought out through the frontal incision, but the wick itself is left in place for four days and then carefully removed. Peet⁹ stated, "The object of this procedure is to prevent meningitis by allowing the brain to become firmly adherent to the lacerated dura thereby effectively closing off the subarachnoid space before organisms passing through from the nose can cause infection."

I have used these accepted procedures with varied success, the one difficulty that I always have encountered in attempting to free the dura from the cribriform plate is that the dura has had a tendency to tear, as Grant emphasized in his discussion of Coleman's paper. The dura, in addition to being thin, is likewise under moderate tension, which prevents the carrying out of proper overlapping of the dura which is necessary for thorough invagination of the meningeal fistulous tract. I have included muscle in the suture line to assure against leakage of cerebrospinal fluid. I have further attempted to assure against recurrence of rhinorrhea by filling the bony defect with Horsley's bone wax (Fig 1c), but in spite of all these precautions, recurrence of rhinorrhea has occurred just as it did in the first case of this series. This failure prompted development of the operation employed in these cases of chronic rhinorrhea, in which cure has been obtained

CRANIOSINUS FISTULA

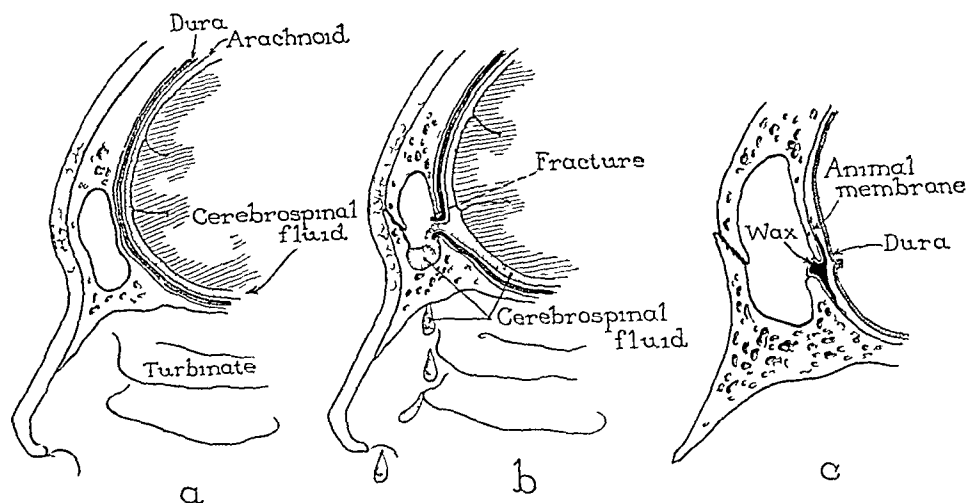


FIG 1a—Normal relationships of the brain meninges and skull in the frontal region, *b*, craniusinus fistula with leakage of cerebrospinal fluid into the frontal sinus and thence into the nose, *c*, plastic closure of the meninges and occlusion of the bony defect with wax.

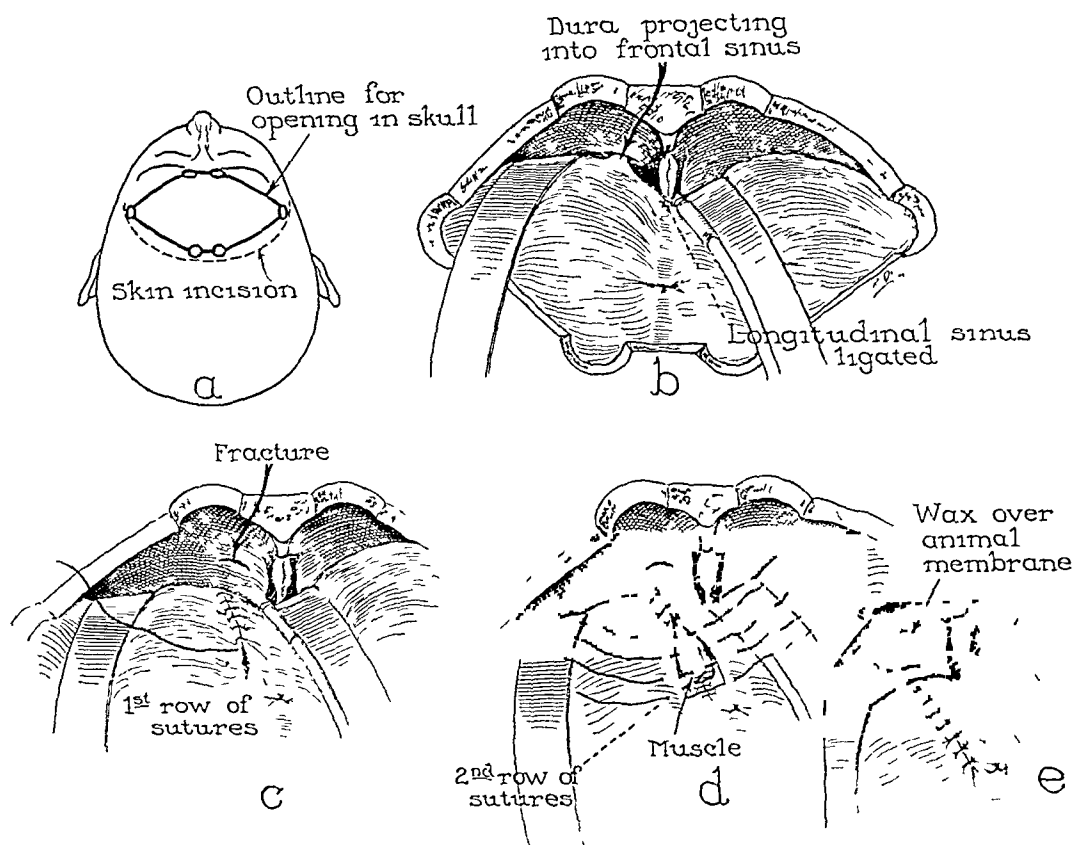


FIG 2a—Schematic outline of incision in the scalp and craniotomy, *b*, elevation of dura, identification of the fistulous tract and ligation of the longitudinal sinus, *c*, closure of the dural tear with a suture of continuous catgut, *d*, reinforcement of the primary closure by means of a second row of interrupted silk sutures including a strip of muscle employed as additional protection against recurrence of the rhinorrhea, *e*, closure of bony opening with animal membrane and bone wax.

The procedure consists of performance of craniotomy which will allow the dura to be elevated from the bone in both halves of the frontal fossa. The bone flap must be designed so as to extend across the midline and to uncover the anterior poles of both frontal lobes (Fig 2a). A coronal scalp-flap incision is employed. It is placed within the hairline, after which the scalp and periosteum are reflected forward to a line just above the frontal sinus. Six trephine openings are made, the first two of which are placed on each side of the midline just above the frontal sinus. The second two trephine openings are placed on each side of the midline and the longitudinal sinus, approximately 3 cm in front of the coronal suture. The third two openings are placed in the temporo-frontal region, one on each side. As the bone between all the openings is cut with a Gigli saw, an opening is effected which is sufficient to permit elevation of the dura and the frontal lobes. The bone flap is kept sterile during the operation by means of a sponge soaked with saline solution. Caution is taken to avoid injury to the longitudinal sinus. Bleeding from the longitudinal sinus is controlled by ligation of the sinus (Fig 2b) with silk ligatures at a level 6 cm above the foramen cecum, which is situated superior to the crista galli. In some instances, it is necessary to ligate the longitudinal sinus where it communicates with the foramen cecum. The advantage of ligation of the longitudinal sinus allows the dura to be sutured into, and, if necessary, to be used in closure of the fistulous tract. The procedure is continued by elevation of the dura from the frontal fossa and the olfactory grooves, where it is necessary to sacrifice the olfactory nerves. The elevation of the dura is continued until the anterior crest of the sella turcica is approached. During this dissection, the fistulous tract is always encountered, whether it be situated on the right or the left side. The meninges will be seen to extend into the defect of the frontal sinus or the cribriform plate.

After the dura has been mobilized sufficiently and the fistulous tract identified, plastic closure of the tract is begun by overlapping of the dura in such a way as to invaginate the meningeal portion of the fistula. The first suture is placed in the most dependent part of the elevated dura (Fig 2c). This suture is continuous chromic catgut No. 0. The primary line of suture is protected by a strip of muscle which is transfixed to the dura and further reinforced by the placing of a second row of interrupted silk sutures (Fig 2d). The defect in the frontal sinus or cribriform plate is filled with Horsley's bone wax. Further to protect against forcing of the wax through the cranial defect into the sinus or nose, Lukens' animal membrane is placed over the defect before the introduction of wax to plug the hole (Fig 2e).

The advantages of bifrontal craniotomy are (1) A better exposure is obtained than by employment of a unifrontal flap, (2) the surgeon is always sure to identify the fistulous tract, (3) the exposure thus obtained affords a better opportunity for elevation of the meninges along the cribriform plate, and (4) after elevation of the dura from the cribriform plate, tension on the dura is relieved, this permits greater ease of invagination of the fistulous tract and successful performance of overlapping dual closure of meningeal defects.

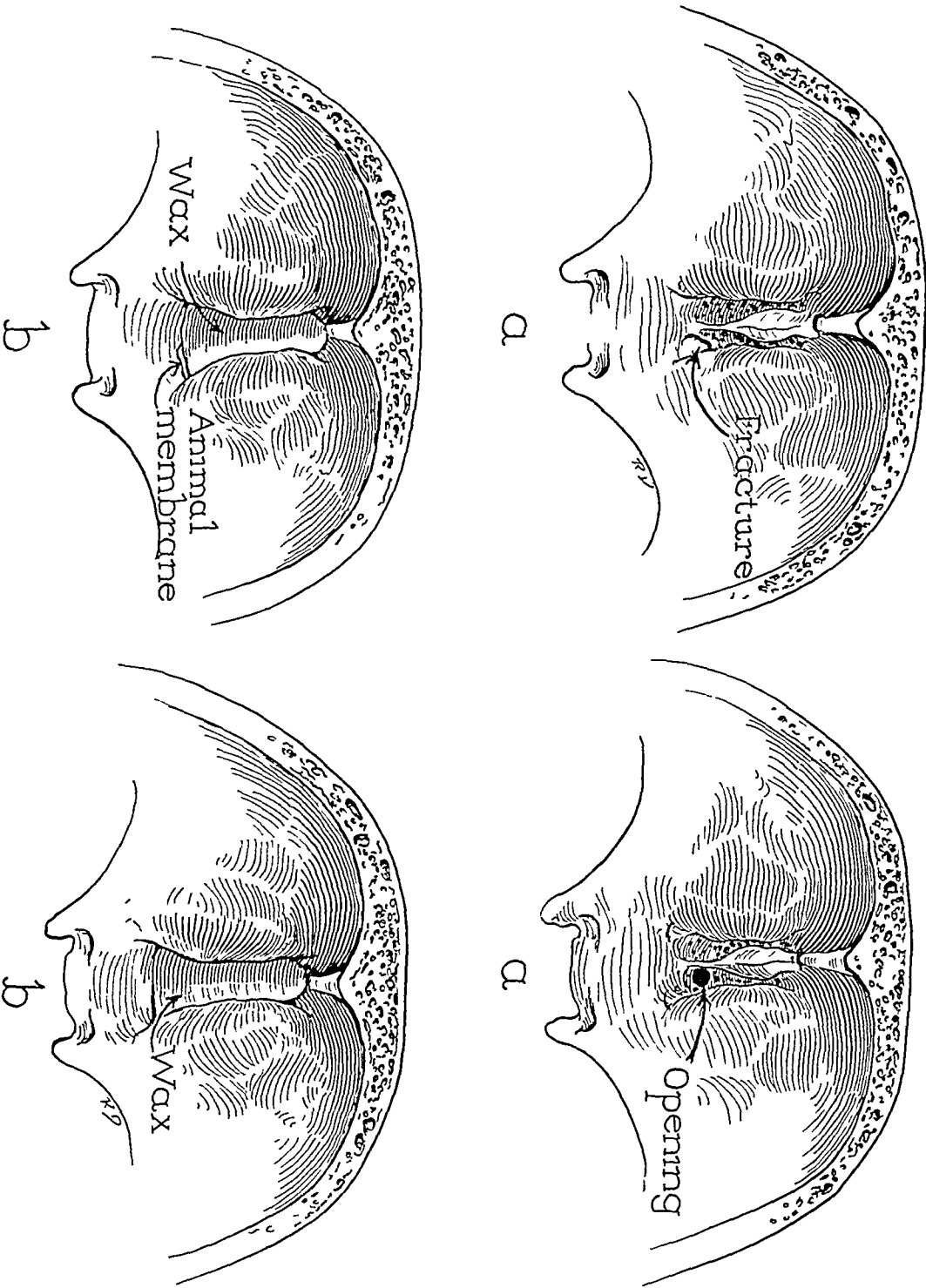


Fig. 3a—Fracture of the cribriform plate, b closure of the bony defect with animal membrane and bone wax

Fig. 4a—Congenital defect of the ethmoid bone such as the third patient in this series had, b, closure of the bony defect with wax

Before replacement of the bone flap, thorough hemostasis should be effected. A rubber tissue drain can be used, but is not necessary because no cerebrospinal fluid will be seen to escape. The bone flap is wired in place with noncorrosive wire, inserted through perforations which are placed opposite each other in the skull and bone flap. The periosteum, galea, and scalp are closed with interrupted silk sutures.

As a precautionary measure, administration of sulfanilamide is continued for three days prior to operation until the concentration of sulfanilamide in the blood reaches a value of from 8 to 12 mg per 100 cc. Likewise, it is continued for ten days after operation, during which time the same concentration of the drug in the blood is maintained. The dosage I have employed, ranged from 45 gr (3 Gm) to 90 gr (6 Gm) per day. In no instance did meningitis develop during the postoperative period.



FIG 5—Postoperative appearance of the patient who had the congenital defect in the ethmoid bone shown in Figure 4a and b.

Comment—Three Cases of Cramosinus Fistulae Results of the method described for plastic closure of a cramosinus fistulous tract have been most satisfactory in all three cases mentioned herein, since all the patients underwent the operation without incident, all incisions healed by primary union, and cerebrospinal rhinorrhea ceased immediately after plastic closure. In the first case, meningitis afflicted the patient (a boy) ten months after operation, after an attack of influenza. This was controlled by chemotherapy with sulfathiazole, and at the present time he is in good health and has been free of rhinorrhea from the date of operation, 17 months ago. The second patient (Fig 3a and b) is well and has returned to work as an engineer in an electric plant and has been free of rhinorrhea for seven months, at the time of writing. The third patient (Figs 4a-b and 5) is well, has returned to normal activity, and has been free of rhinorrhea from the hour of operation, like the others, until the present time, a period of two months. The first patient had had two severe attacks of meningitis prior to his operation. In the second and third cases, in which there were lesions in the ethmoidal plate, the patients had escaped meningitis prior to operation. Postoperative sequelae did not develop in these two cases.

The operative procedure I have described may not be indicated for cerebrospinal rhinorrhea which accompanies acute compound fractures, but it does

offer an effective method for the control of rhinorrhea, especially so for those patients who complain of chronic rhinorrhea in traumatic cases of delayed and spontaneous rhinorrhea. The one objection to this procedure is the loss of the sense of smell which ensues, but if symptoms are to be relieved and the hazard of meningitis is to be minimized it becomes necessary for the patient to accept this particular sequela.

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SURGERY OF HYPERPARATHYROIDISM THE OCCURRENCE OF PARATHYROIDS IN THE ANTERIOR MEDIASTINUM AND THE DIVISION OF THE OPERATION INTO TWO STAGES*

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THE TREATMENT of hyperparathyroidism is surgical. Irradiation therapy has so far proved unsuccessful,† and attempts to control the effects of the disease by diet have been injurious either to the kidneys or to the bones. The surgical treatment of hyperparathyroidism must be precise to meet the challenge of the diagnostician. Spingarn and Geist² have reported two cases in which the diagnosis is beyond question and yet in which no parathyroid tumor was found at operation. Nine patients have been referred to the Massachusetts General Hospital for further operation following unsuccessful explorations by other surgeons. In one of these, Case 50 of our series,‡ the author was unable to find the adenoma at operation, its location was disclosed at autopsy. In the nine cases, the surgical problem has been one of the peculiar position of the tumor. All had large tumors and, from the point of view of size alone, none should have been difficult to find.

The problem of the surgery of hyperparathyroidism involves both site and size of the tumor. As more cases are recognized by the clinicians, size becomes increasingly important. Milder cases are being diagnosed and the milder the case, the smaller the tumor. Unless surgeons take cognizance of the peculiarities of parathyroid surgery, an increasing proportion of surgical failures may be expected. This paper is written to emphasize certain points already described,^{3, 4} and to give in detail newer ideas in the operative management designed to obviate the difficulties which lead to unsuccessful explorations.

REQUISITE TRAINING—The problems of parathyroid surgery are not those of the regional anatomy of the neck but are peculiar to the anatomy and physiology of the parathyroid glands. Special training is needed, the technical skill adequate for successful extirpation of the thyroid gland is not sufficient. The nine cases with previous unsuccessful attempts, mentioned above, were

* Read before the American Surgical Association, White Sulphur Springs, W. Va., April 28-30, 1941.

† Four of the series of cases of hyperparathyroidism in this hospital received adequate roentgenotherapy before removal of the adenoma at operation, in none was there a demonstrable change in the abnormal metabolism. Reports in the literature of cases benefited by roentgenotherapy¹ do not include sufficient data of calcium and phosphorous metabolism for us to assume that the clinical improvement was not due to diet alone.

‡ The numbers refer to the cases of hyperparathyroidism at the Massachusetts General Hospital in the order in which the diagnosis is proven. The same case numbers are used in all publications from this hospital.

operated upon by 13 surgeons, all skilled in surgery of the thyroid gland. Not only were the tumors not found but several of the surgeons intentionally removed what they considered to be normal parathyroid glands, a procedure without justification.

Recognition of Parathyroid Tissue—The eye must be trained to distinguish the varieties of parathyroid tissue. Beyond the variations in the glands of normal people there are differences in the uninvolved as well as the diseased glands of hyperparathyroidism. The training requires prolonged and precise observation and, apparently, cannot be obtained by operating upon the thyroid gland. There is but one place for this training and that the post-mortem table. Here, any debatable tissue must be immediately checked by frozen-section, since by the time permanent sections are ready the image of the gross appearance is forgotten and the chance for experience lost.

The size and shape of the normal gland show considerable variation (Fig 1). The gland is soft, for it is composed of the parathyroid and fat cells, with but little supporting stroma. The capsule is thin, with a fine network of ves-

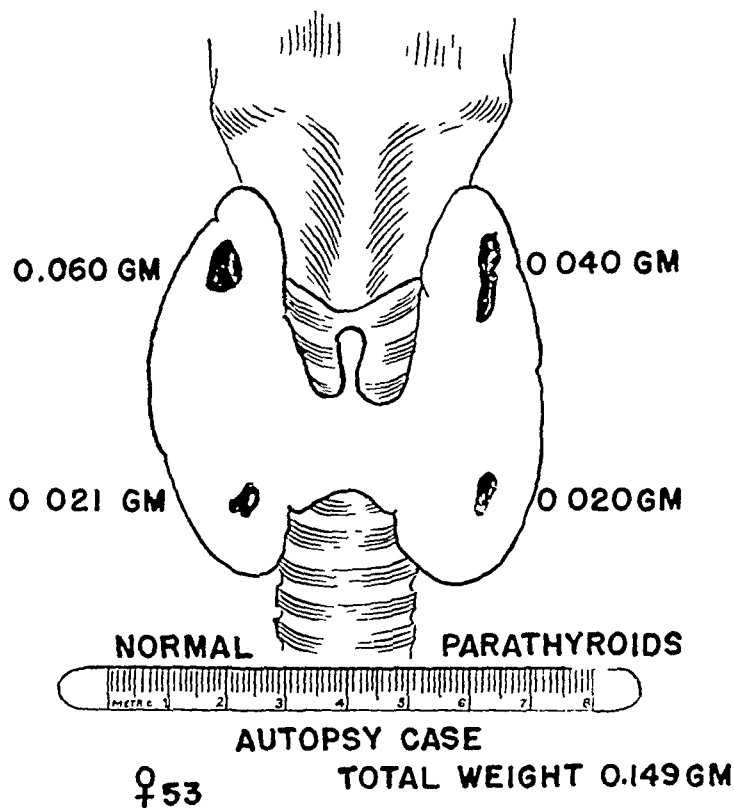


FIG 1—Four normal parathyroids, removed at autopsy, were photographed on a diagram. Variations in shape and size are shown (Churchill and Cope⁴ ANNALS OF SURGERY, 104, 9, 1936).

sels over it. Because of the softness, the shape is determined by the surrounding organs which are firmer. The glands are flat like a pancake only if molded over the surface of an organ like the thyroid or esophagus. If they are free in fatty or areolar tissue they are globular, a form they also assume when within the thymus gland. They have a clearly formed vascular hilus with a fern-like pattern of vessels radiating out over the capsule.

The color of the gland varies, and depends upon the proportion of glandular to fat tissue. The fat content of the normal glands changes with age.⁵ The gland of the child before puberty contains little or no fat and is, therefore, the coffee-brown color of the normal parathyroid cells. After puberty, until about age 40, the fat content increases and the glands, therefore, become yellower. After age 40, there may be a decrease in fat content with almost none in the older age-groups. With increasing experience in the identification of the uninvolved or so-called "normal" glands in patients with hyperparathyroidism due to adenoma, the author has been impressed with the abnormal yellowness. It is believed, though not proven histologically, that, in the presence of an active tumor, there is an atrophy or disuse of gland cells, with a relative increase in the fat cells. Since the uninvolved glands may be so nearly the color of the surrounding fat the only means of distinguishing them is their encapsulated form and vascular pattern.

Both the adenomata and hyperplastic glands contain little or no fat and are, therefore, browner than any normal tissue. Although we have only had experience with six cases, it is believed that the hyperplastic glands are somewhat different from the adenomata, the color is a shade deeper, the surface is uneven instead of smooth, and the gross contours are more irregular.

Meticulous Technique—The importance of a careful, bloodless technique has been stressed in previous publications.^{3, 4} Even the slightest trauma to a parathyroid gland may result in the spread of a subcapsular hematoma, changing the appearance to that of thyroid or an hemolymph gland. Inadequate hemostasis may result in diffusion of blood through the areolar tissue, beclouding the presence of a normal gland or small adenoma. In an operation for hyperparathyroidism there is no place for haste.

Understanding of Parathyroid Physiology—The surgeon should be conversant with the abnormal physiology of the parathyroid glands. The search at operation for parathyroid tissue may be prolonged. The conviction that the patient has hyperparathyroidism may serve to drive the surgeon forward to the goal.

Once the offending gland or glands are isolated, the surgeon must exercise judgment in what to do with them. Not only must he avoid producing hypoparathyroidism but also appreciate the relation of the renal and bone complications of the disease to the tetany of the recalcification period.⁴

WIDESPREAD DISTRIBUTION OF PARATHYROIDS—It is not enough to know what parathyroid glands look like, knowledge of the regions in which they are to be found is equally important. Perhaps the name parathyroid is unfortunate for it suggests that these glands exist only in a limited area near the thyroid. Indeed, this concept has arisen, the initial clinical interest in these glands was occasioned by the desire to avoid them in performing a thyroidec-tomy, and anatomic studies of their distribution were made by men primarily interested in the problems of thyroid surgery. The widespread distribution of parathyroid glands which may occur normally has been a product of embryologic study. This problem of distribution has become clarified in our

minds owing to the number of our cases in which a mediastinal parathyroid tumor has been discovered

Incidence of Parathyroids in the Mediastinum—At the Massachusetts General Hospital there have been 60 cases of hyperparathyroidism. The diagnosis was proven in 58 at operation, in two, at autopsy. In 54, the disease was due to adenoma, in six to primary hyperplasia. Of the 54 cases due to adenoma, four had two adenomata, the rest only one*. This makes a total of

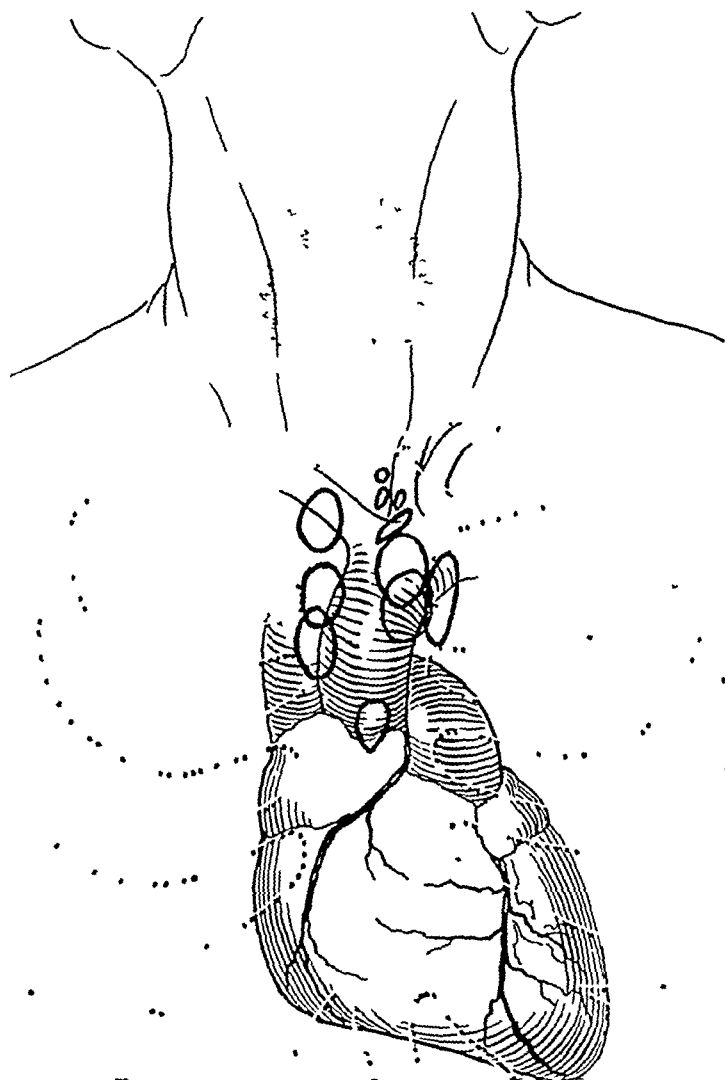


FIG. 2.—Diagram of position and size of the parathyroid adenomata recovered from the anterior mediastinum in 11 patients of this series

58 adenomata, 11 were found in the anterior mediastinum (Fig. 2), and 5 in the posterior, the remainder in the neck. Of the six cases of primary hyperplasia, 23 individual glands were identified at operation, all lay in the neck, except one which was in the posterior superior mediastinum. The twenty-

* Two of the cases with one adenoma already removed show some degree of residual disease and are believed to have another adenoma, in the mediastinum. The second-stage operation has been postponed.

fourth gland, which was not disclosed (Case 15), presumably lay in the anterior mediastinum *

Of the nine cases previously operated upon by other surgeons and referred to this hospital for further operation, in six, the adenoma was found in the anterior mediastinum, in one, in the posterior, in only two, were the adenomata in the neck. The position of the adenoma within the chest in seven of the cases presumably accounted for the failure of the search. From a statistical point of view, the nine cases constitute a selected group, and should be eliminated from consideration of the probable incidence of parathyroids within the mediastinum. With these nine cases excluded, nine of 49 adenomata (18 per cent) were in the mediastinum, five (10 per cent) were in the anterior mediastinum, four (8 per cent) in the posterior.

Reasons for Mediastinal Position—There are two causes for the presence of parathyroid enlargements within the mediastinum.

(1) EMBRYOLOGIC DESCENT—In the series of patients with hyperparathyroidism at this hospital, parathyroid glands have been encountered from 1 cm. above the upper pole of the thyroid gland down into the mediastinum as far as the pericardium. These extremes in distribution are accounted for by the embryologic development of the parathyroid glands. Excellent accounts of the embryology of the parathyroid glands and their associations with the development of the thyroid and thymus glands are given in the monographs by Weller,⁶ and Norris.⁷

The parathyroid glands develop as two pairs from two separate bilateral primordia in conjunction with the thyroid and thymus glands. The development of the so-called upper pair of parathyroid glands is the simplest. They have their origin in a primordium arising from the fourth branchial cleft. The parathyroid cells appear above and behind the lateral thyroid component arising from the same cleft and descend in this relation to the lateral thyroid as it grows down in the neck to join the median thyroid component. Since the lateral thyroid component travels only a short distance during embryonic life, from just below the upper portion of the larynx to the normal thyroid position opposite the cricoid cartilage, the parathyroid IV (upper parathyroid of adult life) also travels a short distance only. The upper parathyroid of the postfetal human being, from the embryologic point of view should, therefore, exist only in an area bounded above by the upper border of the larynx and below by the lower pole of the thyroid. Theoretically, they should not occur as low as the lower pole of the thyroid.

In actual observation of patients at operation, in which it has been possible to identify definitely the upper from the lower parathyroid, only once has a normal upper gland been disclosed below the main branch of the inferior thyroid artery. It is often encountered in the upper branches of the inferior thyroid vessels but more often lies nearer the upper pole. Embryologically, it should be situated posterior to the thyroid but actually this is not always

* This patient died at home, presumably of cardiac failure, no postmortem examination was obtained.

the case In two patients, the upper glands have been isolated anterior to the superior thyroid vessels, one adenoma and an occasional normal gland have been revealed between the upper pole and the larynx Largely because of the limited area of embryologic descent, the upper parathyroids have been much easier to identify surgically (Fig 3)

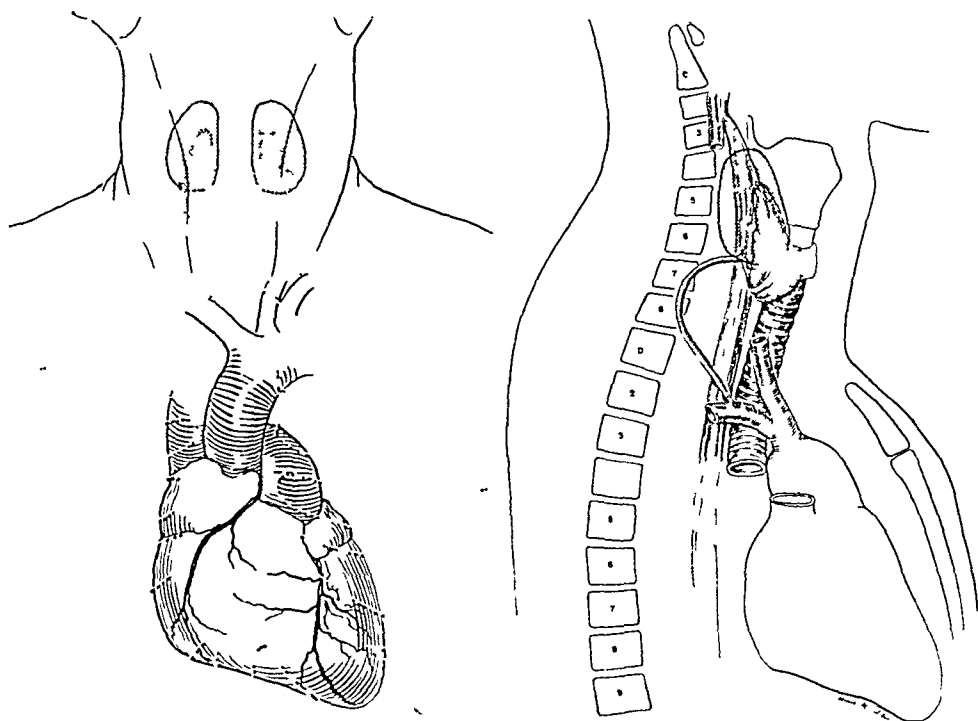


FIG 3—Lateral and anterior views of area of occurrence of upper parathyroid (IV) due to embryology The shading shows the extent of possible positions of the upper parathyroids due to differences in development during fetal life The limited area facilitates the surgical identification of these parathyroids

Not so the lower parathyroids In their embryologic development they cover a wide field and their discovery in postfetal life presents the major surgical difficulty of hyperparathyroidism The lower parathyroid develops on either side from the third branchial cleft in close proximity to the primordium of the thymus gland As the thymus tissue grows and moves downward in the neck from the pharynx to its final position in the anterior mediastinum, the parathyroid tissue descends with it Such is the proximity of this parathyroid to the thymus that Weller⁶ has well called it the “parathymus” gland In the majority of cases examined by embryologists, these parathymus glands pass with the thymus lateral to the upper parathyroid and lateral thyroid component and are dropped off opposite the lower pole of the thyroid The thymus continues its growth into the thorax Sometimes, however, the parathymus gland grows with the thymus on beyond the lower pole of the thyroid and deposits itself either low in the anterior neck or in the chest The association may end with the parathyroid still within the capsule of the thymus

Reports have appeared⁸ of intrathymic normal parathyroids in the human being We have seen no reports of parathyroid tumors within the thymus

The intrathoracic tumors reported in the previous communications from this hospital^{3 4} were free in the areolar tissues of the mediastinum and not within the thymus. Of the five subsequent tumors excised from the anterior mediastinum, three were within a well-defined thymic capsule. The intrathymic existence of the parathyroid gland is more common, we believe, than previously suspected. It is important to stress that parathyroids are to be found not only in the upper portion of the thymus as one would expect on embryologic grounds but also in the lower portion as well (Case 50, Fig 11)

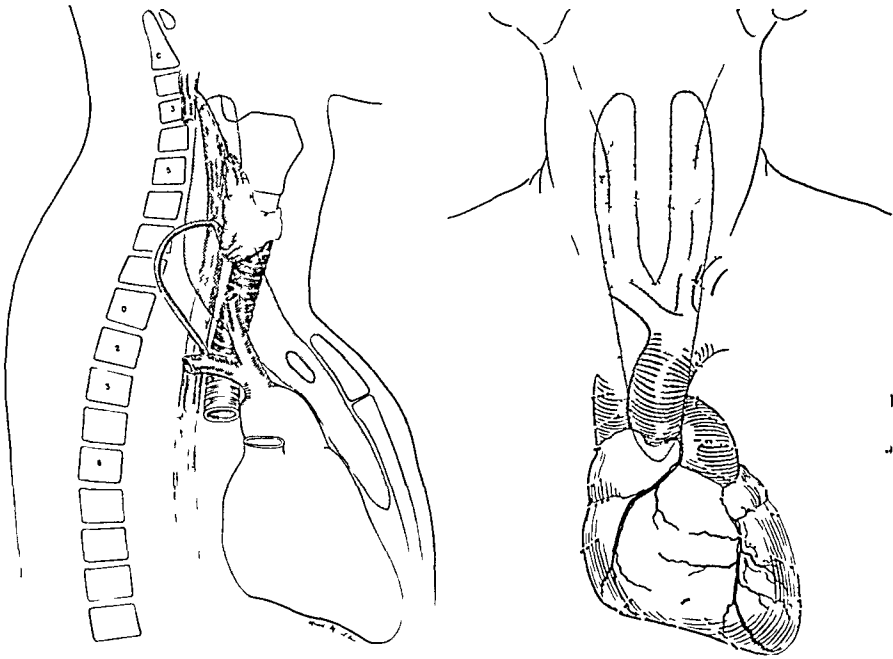


FIG 4—Lateral and anterior views of area of occurrence of lower parathyroid (III) due to embryology. The shading shows the extent of possible positions of the lower parathyroids due to differences in development during fetal life. The extensive area accounts for the surgical difficulty frequently encountered in identifying these glands. The glands lie anterior or posterior to the left innominate vein.

The parathyroid gland in this patient was in the lowest position of any gland we have observed. A gland outside of the thymus might, theoretically, be in a similarly low position. It is possible, though doubtful, that parathyroid tissue might descend lower than the thymus, since the position of the thymus in the anterior mediastinum is variable, the lowest point at which parathyroid tissue might be encountered is also variable. The area in which the lower parathyroid gland is to be expected on an embryologic basis is shown in Figure 4. The uppermost level is theoretically higher than that of the upper parathyroid. No upper gland has been observed in our series above the upper pole of the thyroid.

The relations anteriorly and posteriorly are shown in the illustrations. In its descent, the thymus tissue passes anteriorly to the great arteries but not necessarily to the innominate veins. At three operations, at which the thymus could be definitely identified, it encircled the left innominate vein but lay in

front of the aorta, the innominate, and carotid arteries. The parathyroids in the anterior portion of the superior mediastinum have borne this same relation to the great vessels. In the anterior mediastinum proper, only those glands that were within the thymus have actually lain in front of the aorta. Those lateral to the thymus have dropped posteriorly into the middle mediastinum, lateral to the aorta.

Reports have appeared^{9, 10} emphasizing the occurrence of parathyroid tumors within the substance of the thyroid gland. Embryologically, the upper parathyroid could, theoretically, be included within the thyroid, much as the lower parathyroid is caught in the thymus. Such a position within the thyroid is less likely to be assumed by the lower parathyroid, it might, however, get caught in the sulcus of the expanding thyroid. Indeed, we have not infrequently found both upper and lower parathyroids deep in sulcuses of the thyroid, even completely buried from view, but we have not observed a true intrathyroid parathyroid, normal or tumor.

(2) DISPLACEMENT FROM NECK INTO MEDIASTINUM.—It is believed that enlarged parathyroid glands may be displaced from their position of embryologic development in the neck into either the posterior or anterior portions of the superior mediastinum. No gland has been followed through such a trek but the assumption is made on the basis of indirect observations. First, enlarged parathyroid glands have been found in the posterior mediastinum where, embryologically, no parathyroid tissue should exist. Second all of the enlarged parathyroids encountered in the posterior mediastinum have had long vascular pedicles leading up to one or other group of thyroid vessels. In contrast, the blood supply of enlarged parathyroids in the anterior mediastinum occurs locally with no connection to the thyroid vessels. For example, in Case 57 the arterial supply arose from the middle mediastinum along the pleura, with the main venous return emptying into the left innominate vein, in Case 54 the artery came from the pericaudal vessels, with the largest vein again leading up into the innominate.

Third, no normal gland has been found straying far from its vascular base. The normal gland is supplied by a fine twig from the nearest artery, if the gland lies near the upper pole of the thyroid, the twig comes from the superior thyroid artery or one of its branches, if near the lower pole it originates in a branch of the inferior thyroid artery, if between upper and lower poles, the parathyroid artery may come from the anastomotic branch between superior and inferior thyroid arteries. It is, therefore, believed that the normal parathyroid receives its blood supply from the region in which the gland was finally deposited during embryologic development and that the origin of the arterial supply should give the clue to this region if the gland were displaced.

Fourth, the parathyroid gland is held in position largely by its vascular pedicle. The capsule has only filmy connections with the surrounding tissues and unless caught in a sulcus, for example in the thyroid, the gland is movable. This is in contrast to the thyroid gland which has firm fascial attachments to the cricoid cartilage and upper trachea which cause it to move with larynx.

and trachea on swallowing. When a parathyroid gland enlarges, it can be readily displaced by the surrounding organs. The vascular pedicle should offer but little resistance to downward displacement. Thyroid enlargements when freed of fascial attachments by continued growth are readily drawn into the mediastinum in spite of their vascular connections.

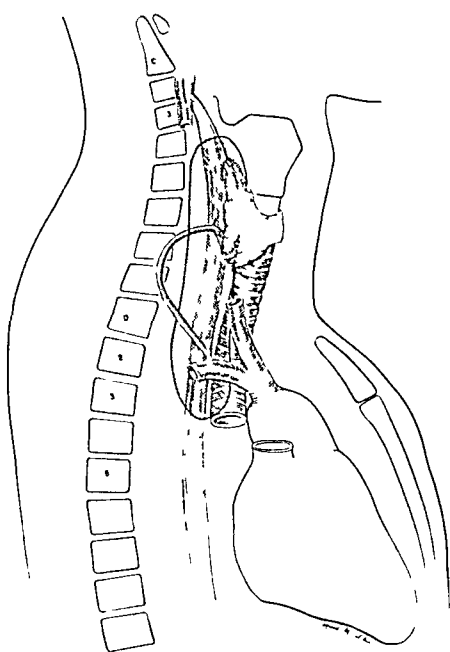


FIG 5

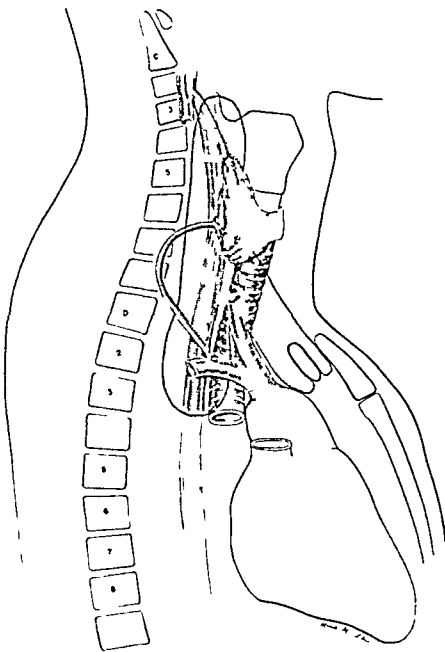


FIG 6

FIG 5—Lateral view of area of occurrence of enlarged upper parathyroid (IV). The original area of embryologic occurrence (Fig 3) is added to owing to displacement downwards of enlarged glands. Because the only embryologic position permitting displacement is the posterior one, enlarged glands move toward the posterior superior mediastinum.

FIG 6—Lateral view of area in which enlarged lower parathyroids (III) displaced from their original position in neck may be found. Glands having had embryologic position posterior to thyroid after enlargement may be displaced into posterior mediastinum; those having had embryologic position caudal to thyroid in a more anterior plane, may be displaced into the anterior superior mediastinum.

Fifth, three times an enlarged upper parathyroid has been disclosed straddling the inferior thyroid artery like a saddle on a horse's back, it is believed that the gland was caught by the artery on its journey.

The passage of an enlarged parathyroid downward is presumably initiated by the weight of the gland itself but is accelerated as it approaches the thorax by the negative intrathoracic pressure. Depending upon the original position of the gland, the enlarged gland may be sucked into either the posterior or anterior mediastinum. If the gland was originally an upper one, it passes downward into the posterior mediastinum if it is not caught on the inferior thyroid artery (Fig 5). If the gland was originally an inferior parathyroid lying posterior to the lower pole, it also will be sucked into the posterior mediastinum. If, however, it lay caudal to the thyroid lobe, in which case it will be in a more anterior plane, it may be drawn into the anterior superior mediastinum (Fig 6).

Walton¹¹ was the first to describe the probable descent of enlarged parathyroids from neck into mediastinum. He conceived of various fascial planes which decided whether the enlarged gland descended into the posterior or anterior position. We have been unable to confirm the existence of these fascial planes and believe that the direction taken is due rather to the original position of the gland as a result of its embryologic development. Once these glands have reached the mediastinum they presumably do not go any further since the negative intrathoracic pressure no longer exerts a pull upon them.

The distribution of parathyroid glands may be summarized as follows. The upper glands (IV), when normal, exist in a limited area near the upper thyroid gland, when enlarged they may be displaced toward the posterior mediastinum, surgically they are easy to find. The lower glands (III), sometimes called the parathymus glands, when normal, are to be found over a wide area, from larynx to anterior pericardium, when enlarged this area may be increased to include the posterior superior mediastinum, then identification may require extended search. Enlarged parathyroid glands may exist in the mediastinum in more than 10 per cent of cases of hyperparathyroidism, and the surgeon must be prepared to meet this eventuality. Although a vascular pedicle leading to the mediastinum should be sought when exploring the thyroid region, its absence does not exclude a parathyroid in the anterior mediastinum.

OPERATIVE TECHNIC—The not infrequent presence of parathyroid glands within the mediastinum has necessitated a reconsideration of the operative plan. Although early in our experience we met with some success in delivering enlarged parathyroids from the mediastinum by blunt dissection with the fingers, later failures emphasized the importance of direct visualization of tissues. The neck is first explored as heretofore, and if all of the offending glands are not disclosed the anterior mediastinum is opened through the sternum at a second operation.

First Stage—Exploration of Neck and Posterior Mediastinum The regions of the neck and posterior superior mediastinum in which parathyroids may be found, can be explored adequately under direct vision through a wide collar incision in the lower neck. The platysma is elevated with the skin flaps. The sternomastoid muscle is dissected free of the sternohyoid and omohyoid muscles opposite the cricoid cartilage but only enough to expose the ansahypoglossal nerve. The sternohyoid muscles are divided in the midline from the thyroid cartilage to the manubrium. Stitch ligatures are placed around the larger veins lying in the fascia on the anterior surface of the sternohyoid muscle. The muscle is cut from medial to lateral. The small artery lying near the medial border is ligated. The sternothyroid muscle is thus exposed and it is divided at its insertion to the larynx. The ansahypoglossal nerve is spared as it passes along the posterolateral border of this muscle to supply the lower portions of both the pretracheal muscles. Retraction sutures are placed through the upper end of the outer muscle only and the lower ends of both muscles, retracting them from the thyroid gland.

Large clamps are no longer used in dividing the pretracheal muscles, since to some extent their insertion is blind and the fine vessels leading directly from the surface of the thyroid into the sternothyroid muscle may be torn, with resulting hemorrhage. Wider exposure is obtained by retracting the entire sternothyroid muscle downward. Healing is better since the amount of necrosed muscle is decreased.

Before division of the pretracheal muscles, the contours of the thyroid prominence are carefully inspected. If there is any apparent difference, the larger side is exposed first. Such a difference due to a parathyroid tumor is rarely seen, it is more often due to asymmetry of the thyroid. In the absence of a demonstrable tumor mass directing attention to a special area, one lateral thyroid lobe is exposed. Traction sutures of silk rather than hooks are placed in the thyroid. In exposing the thyroid, pains should be taken to get in the fascial plane as near the true thyroid capsule as possible. If too much areolar tissue is left over the surface of the thyroid, parathyroid tissue may be retracted with the thyroid and difficulty encountered in exposing the thyroid sulci.

The search now proceeds on the basis of likelihood. Since the upper parathyroids occur in a smaller area it is sound policy to look for this gland first, it should be sought in the region from the inferior thyroid artery up to and above the upper pole. The gland may lie on the lateral, posterior, or medial surface*. Both the superior and inferior laryngeal nerves may be exposed. If the upper gland is not revealed on the initial search, the region of the lower pole is next explored. If an apparently normal upper parathyroid was isolated, it is wise to proceed to the opposite side of the neck and look for the corresponding upper gland before exploring for the lower gland of the same side. This shift of side is made because of the probability that the glands are arranged symmetrically (see page 722), *Symmetry of Position*, and it may thus be possible to uncover rapidly 50 per cent of the glands.

When the regions of the lateral thyroid lobes have been thoroughly searched without finding the offending gland or glands, the dissection is then widened. The area above the upper pole as high as the upper border of the larynx is opened and the areolar tissue as far lateral as the carotid sheath is explored. The carotid sheath itself should be inspected†. The esophagus should be examined because a gland may hide behind it or between it and the trachea. The absence of a vascular pedicle along the esophagus is usually sufficient evidence to exclude a gland. In this plane, the sympathetic nerve trunks are uncovered. Next, the dissection is carried down into the posterior superior mediastinum on

* Parathyroid glands have been reported on the anterior surface of the thyroid gland¹². We have never encountered them in this position. It may be that a parathyroid gland on the lateral surface of the thyroid may assume an anterior position as a goiter develops.

† Norris⁷ believes it possible on embryologic grounds for parathyroid tissue to become included within the carotid sheath. Although the sheath has frequently been opened in the cases operated upon at this hospital, no parathyroids have been encountered in this position.

either side, a feat easily accomplished since the line of vision is direct. On the left side, it is wise to identify the thoracic duct in order to avoid injuring it. Finally, the anterior superior mediastinum is sifted but only as far as direct visualization and dissection with instruments is possible.

CONSIDERATIONS PECULIAR TO FIRST STAGE—*Vascular Pedicles* The use of the identification of vascular pedicles leading into the superior mediastinum has already been pointed out. Such a pedicle leading in an atypical manner from one of the thyroid arteries may give an immediate clue to the position of a diseased parathyroid. In Case 53 the right upper parathyroid, an uninvolved gland, had been identified, the left upper was not present in the symmetrical position. A small arterial twig, however, was seen leading up from the anastomotic artery to the space between thyroid and larynx where no artery normally runs. Dissection of the posterior thyroid region revealed no parathyroid tissue. Pursuing the vascular pedicle, the thyroid was separated from the larynx and upper trachea anteriorly and a small, flattened adenoma promptly found.

Thymic Rests Rests of thymus tissue may also be a clue pointing to parathyroid tissue. These rests are not uncommon in the neck as well as mediastinum, and are due to remnants of tissue dropped off as the thymus descends from primordium to mediastinum. Since these rests are presumably pieces of the uppermost portion of the developing thymus, that portion with which the parathyroids III are closely associated, parathyroid tissue may adjoin if not lie within their capsule. Thymus rests should never be resected until it is certain that no parathyroid tissue is enclosed within them.

In addition to isolated remnants, there may be a well-defined tongue of the thymus gland rising toward the lower pole of the thyroid from the anterior mediastinum. In Case 47 after the identification of three normal glands, the adenoma was found within the capsule of such a tongue. In another patient, a normal gland lay within a tongue of thymus. In a patient recently operated upon for hyperthyroidism, rests of thymus tissue were encountered on either side behind the upper poles of the thyroid. Normal parathyroid glands were identified, one outside the thymic capsule and one within.

Subtotal Resection of the Thyroid If the capsule and sulci of the thyroid gland have been carefully explored, actual resection of the thyroid gland should rarely be necessary. As mentioned above, under Embryologic Descent (page 710), parathyroid tissue, theoretically, may occur within the true capsule of the thyroid gland, none has been seen in this position in this hospital. Normal and enlarged glands have been found deeply buried in sulci but they have been outside the true capsule of the thyroid. It is possible that some of the "intra-thyroid" parathyroids reported in the literature may have been placed in a position similar to ours.

Second Stage—Exploration of Anterior Mediastinum The anterior mediastinum cannot be explored under direct vision through an incision in the neck. The plane of the anterior space beneath the sternum lies at a right angle to the surgeon's line of vision. The only way to see into the anterior mediasti-

num is to open into it through the sternum. Adequate exposure of the anterior space is obtainable through division of the midline of the sternum from the notch of the manubrium to the level of the third interspace.

The skin is incised from the neck scar to below the third interspace and the midline of the sternum exposed. The pretracheal fascia is divided in the midline just above the manubrial notch and separated from the posterior periosteum of the manubrium. A finger is then inserted posterior to the manubrium

and worked downward behind the sternum, pushing the pleura laterally and creating a space for cutting the sternum. On one side an opening, medial to the internal mammary vessels, is made into the cavity behind the sternum from the third interspace, and again, by blunt dissection, the pleura reflected laterally. The tunnel starting at the manubrium is now connected with the third interspace. The sternum is cut with a Lebsche sternal knife (Fig 7), an instrument preferable to the Gigli saw, bone cutters, or longscissors. The sternum is divided into two or three portions, depending upon the exposure needed. By incising from manubrium to the third interspace on one side, a good view of that side

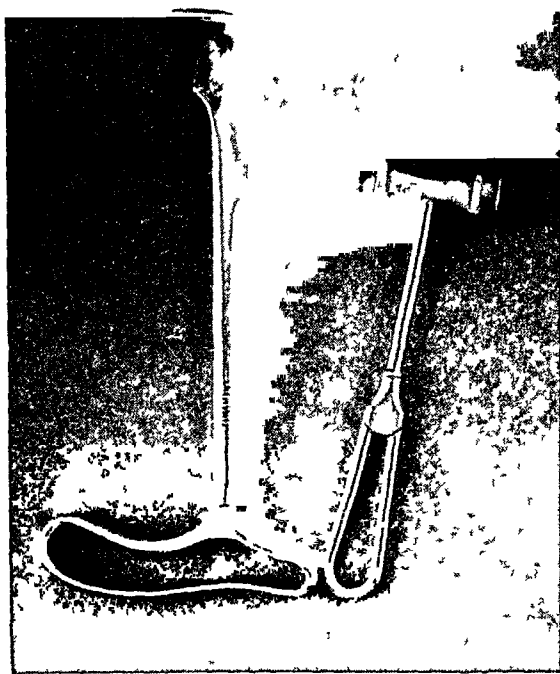


FIG 7—Lebsche sternal knife with mallet used for cutting the sternum

of the anterior mediastinum can be obtained (Figs 8 and 9). If the parathyroid gland is not found on that side, the third interspace of the opposite side is exposed and the sternum divided into it also. By this cut, the sternum is divided into three pieces and a wider exposure of the mediastinum obtained (Fig 10). The longitudinal halves of manubrium and upper body of the sternum form two of the pieces and are retracted laterally. The lower undivided body is the third part and can be pulled downward and outward to expose the anterior pericardium. This third part with its attached costal cartilages forms the keystone of the anterior arch of the chest. Splitting of the sternum further down the midline diminishes the stability of this arch and the added exposure is not required.

The angle of the cut in the sternum from midline to third interspace is best made at 45 degrees. If both interspaces have to be opened into, the inverted V formed will aid the immobilization of the sternal fragments on closure.

After dividing the sternum, strict hemostasis must be secured by use of bone wax and silk sutures before any dissection is carried out within the

FIG 8—Initial cut of sternum partially made using sternal knife. Incision was started in right third interspace running towards notch of manubrium (Case 55, retouched photograph of operation). Insert is diagram of incisions of sternum



FIG 9—Anterior mediastinum exposed by retracting sternum after initial cut. View limited to the right side (Case 55)

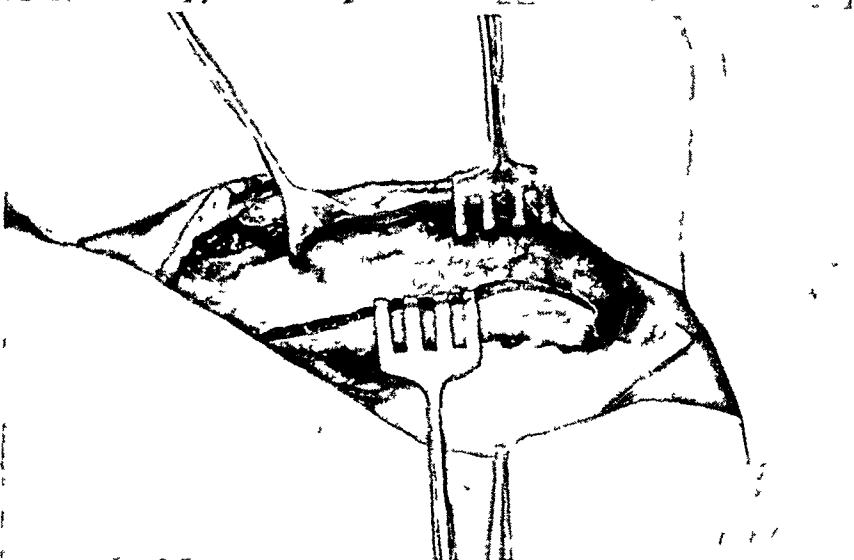
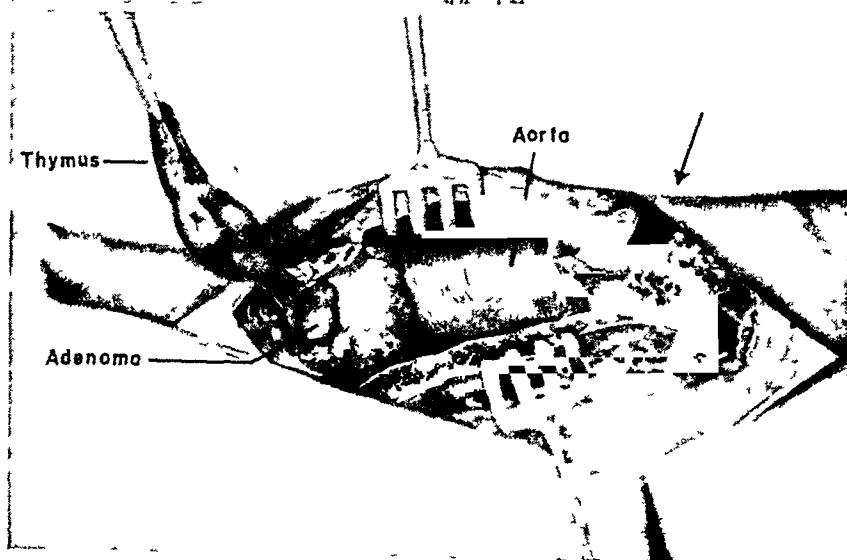


FIG 10—Exposure of anterior mediastinum increased by second cut of sternum into left third interspace. Arrow points to cut. The thymus gland is retracted out of the operative field. The parathyroid adenoma, dissected out of the thymus capsule, lies at the base of thymus on a pad of mediastinal fat. The aorta is shown between the retractors, caudal to the fat pad (Case 55)



thorax The same particular technic used in the exploration of the neck must be employed, otherwise a small adenoma will be overlooked

In the first dissection, the pleura on both sides is identified and displaced laterally The great vessels are then uncovered, the remnant of the thymus should be encountered

As far as we know now, the extent of the search within the mediastinum should be from the neck down to the right auricle and upper reflections of pericardium The tumors are not found merely in the actual anterior space but may be displaced posteriorly on either side of the aorta, lying actually in the middle mediastinum against pleura and lung root The tumors have been both anterior and posterior to the innominate vein Apparently this vein lies in the middle of the path of embryologic descent of both thymus and parathyroids, whereas the arteries lie posterior

In order to prevent as much postoperative discomfort as possible the sternum should be sutured firmly The best closure has recently been obtained with stainless steel wire, which has sufficient tensile strength to be drawn tight and yet can be manipulated with ease

On closing, all air and fluid should be removed from the mediastinum by suction and the absence of pneumothorax confirmed clinically, or roentgenologically if there is any doubt Closure is made without drainage

The anesthetic of choice for both operations is intratracheal gas-oxygen-ether In the second, provision for positive pressure is made

CONSIDERATIONS PECULIAR TO SECOND STAGE—*Exploration Defined by Thymus* Much time may be saved by exposing the thymus gland In the first place, parathyroid tissue will probably not occur lower in the chest than the thymus and once the lowest point of the latter has been determined, at least the first dissection should be done from there upward In the second place, normal parathyroids and parathyroid adenomata may be found within the thymus capsule, the adenoma in three of our cases has been so situated One of these was not discovered until the portion of thymus lying behind the left innominate vein was freed In the third place, since the parathyroids descend in intimate relation to the thymus gland in embryologic life, if a parathyroid is not within the thymic gland substance it may be expected to be close by

In exposing the thymus, care must be taken not to resect it or jeopardize its blood supply unless it is certain that it contains no normal parathyroid tissue The warning against resecting normal parathyroids applies, therefore, to resecting the thymus (see page 722), Uses of Exposed Uninvolved Glands)

CONSIDERATIONS APPLICABLE TO BOTH STAGES—During either operation the following observations should be kept in mind

ANTICIPATION OF SIZE OF ADENOMA The surgeon may anticipate the probable size of a parathyroid adenoma by study of the abnormal physiology of the patient We know of no clue as to whether an adenoma or primary hyperplasia will be encountered The size of an adenoma is, however, roughly

proportional to the elevation of the blood serum calcium. If the elevation is minimal, with a level of 11 to 12 mg, and with a lowered blood phosphorus, the surgeon should realize that any adenoma will be small and may be hard to find. If the blood calcium is 14 mg, the problem is much easier for the tumor should weigh one-half or more grams. If the blood calcium is 15 mg, or above, the tumor may be large enough to palpate or to displace other organs and may be discovered rapidly. The converse is true, if a small adenoma is identified in a patient with a moderate or high elevation of the blood calcium level, a second adenoma exists and should be looked for.

The weight of the glands in primary hyperplasia has not borne such a constant relation to the blood calcium level, variations in the size of the glands in the same patient have been considerable.

The significance of the ability to anticipate the size of a possible adenoma is revealed in still another way. If a large parathyroid mass is encountered in a case with a mild degree of the disease (only slightly elevated blood calcium level), it is probable that the surgeon is not dealing with adenoma but with primary hyperplasia. The gland should, therefore, be inspected for the other characteristics of hyperplasia and the blood supply not damaged, for this may be the gland most favorably situated for subtotal resection.

MULTIPLE ADENOMATA Four of the 54 cases of hyperparathyroidism due to adenoma, in this hospital's series, have each had two adenomata. In two cases, both adenomata were disclosed at the first operation. In the third, a minute adenoma was overlooked at the first operation when the larger adenoma was removed, residual disease required a secondary operation. In the fourth case, the disease was completely relieved for four years after the removal of the first adenoma. In the fifth year, the signs of a mild recurrence appeared and, at a second operation, a small adenoma was found. There are, in addition, two other cases in which one adenoma has already been removed, with a mild degree of the disease, presumably the result of a second adenoma. In one of these the disease was completely relieved for a period of more than two years after the first operation, in the other, there has been continuous disease since the removal of the first adenoma.

From these statistics, therefore, based on the incidence in this series of 54 cases, one would expect that approximately one case in ten of hyperparathyroidism due to adenoma will have more than one adenoma present. The criteria for seeking a second adenoma must be weighed by the surgeon. The surest way of excluding a second adenoma would be to isolate all four glands at the initial operation and, perforce, this may be necessary since one adenoma may not be discovered until after the three uninvolved glands.

It would be unwise, however, to prolong the operation unnecessarily in the majority for the exception. The principles which guide us in making the decision to seek a second adenoma at the same operation in which one adenoma and not all four glands have been found, are as follows.

The size of the adenoma in proportion to the degree of the disease is pri-

mary in importance (see page 720, Anticipation of Size of Adenoma) Since this proportion is only approximate, other considerations enter in

If an adenoma, the adequacy of the size of which is debatable, is uncovered on the first side of the neck explored, it is wise to look for the second gland on that side. If this gland turns out to be uninvolved, it is reasonable to stop with resection of this single adenoma, anticipating that the disease will be relieved. If disease persists, the other side can be explored unhampered by scar tissue and with the knowledge that another tumor must exist. If both sides of the neck had to be explored to find an initial and probably inadequate adenoma, a second should be sought and a complete first-stage operation performed if necessary. Scar tissue makes reexposure so difficult that no field should be closed until it has been completely searched. Having failed to find the second adenoma at the first stage, the second stage will be indicated.

USES OF EXPOSED UNINVOLVED GLANDS Scrutiny of an uninvolved gland exposed during the course of an operation may yield much information of service in directing the surgeon's further attack.

Size and Shape In mild cases, the adenoma may be so small that it is embedded within a capsule of normal parathyroid tissue. Even though wide variations occur among normal glands, comparison of the size and shape of this gland with those of other apparently uninvolved glands may yield the only clue to the presence of the adenoma.

Color In a gland of normal size and shape, a color yellower than expected tends to confirm the presence of an adenoma in another gland. A normal color of a gland slightly larger than normal suggests either that it hides an adenoma beneath the surface or is a secondary hyperplastic gland.

Symmetry of Position In about 80 per cent of patients, the corresponding parathyroid glands occupy symmetrical positions in the two sides of the neck. If the first gland exposed is normal, it may be more efficient to proceed immediately to the symmetrical position on the other side rather than to prolong the search on the same side for the other gland of which there is no definite clue.

Parathyroid III or IV As soon as a normal parathyroid is identified, it should be decided whether it is an upper or lower gland. If it is an upper (IV), any further dissection on that side should be below it, if it is a lower (III), presumably the upper will be higher. Accurate decision may be impossible when the gland lies in the branches of the inferior thyroid artery but careful search for the origin of the gland's arterial supply may furnish the lead. As pointed out above, under *Exploration Defined by Thyroid*, the presence of any thymic tissue in proximity identifies it as a lower gland even if in an upper position.

Exclusion of Hyperplasia The finding of one normal gland excludes primary hyperplasia. This simplifies the problem, for although it may be necessary to identify other normal glands if the adenoma is smaller than expected, in the majority of cases it will not be necessary to identify all parathyroid tissue.

HYPERPLASIA Primary hyperplasia of all parathyroid tissue must be ex-

cluded when an enlarged parathyroid gland has been uncovered. If the gross characteristics are not sufficiently clear for identification and no other gland has been found for comparison, a piece should be removed and examined by frozen-section. The surgeon should not close until the decision in regard to the pathologic type of the disease is definite.

IDENTIFICATION OF GLANDS BY BIOPSY If in doubt whether a piece of tissue is parathyroid, a specimen should be removed for biopsy. *Under no circumstances should the tissue be resected until it is proven an abnormal gland.* Eight surgeons, operating upon patients later sent to us for secondary exploration, removed tissue about which they were undecided. Some avowedly removed what they considered to be normal parathyroid glands. In each of three of the patients two normal parathyroids were actually removed. In these patients, had the adenoma, when found, been resected in entirety, only one normal gland at most would have been left to maintain parathyroid function. Since the viability of this remaining gland might have been jeopardized by operative trauma, if it was not unwittingly excised, a subtotal resection of the tumor was necessary. Since the removal of a small piece for biopsy by frozen-section is simple and a trained pathologist's report dependable, the procedure should be resorted to more frequently.

SUPERNUMERARY GLANDS The possibility of more than four parathyroid glands in one individual menaces the surgeon's peace of mind. Although the text-books of anatomy definitely give four as the normal number of glands, pathologists have described as many as seven in a given individual, many authors have found less than four. The adequacy of the search is always open to question when less than four have been found. No one man has made a sufficient number of extensive dissections to show the real incidence of more than four glands in one individual. Embryologists are agreed that supernumerary glands can occur just as there may be detached remnants of thyroid or thymus in the neck.

In a small series of dissections, the author has encountered five normal glands twice. In one patient with hyperthyroidism, he has uncovered three normal glands on one side, proven by biopsy. From the practical point of view in dealing with hyperparathyroidism this single operative and limited dissection experience must be considered fortuitous. A working plan has been developed. If four normal glands, proven by biopsy, are isolated in a patient with a borderline degree of hyperparathyroidism, and particularly if these glands are symmetrically placed in characteristic positions, no search is made for a possible fifth gland. If, on the other hand, the diagnosis is irrefutable, a further attempt should be made. If the diagnosis in the patient is in doubt and the glands are asymmetrically placed, a possibly asymmetric fifth gland should be sought. Other signs of irregularly developed glandular tissue, such as a pyramidal lobe of the thyroid or thymic rests, would strengthen this decision to look further.

SUBTOTAL RESECTION Subtotal resection of the parathyroid tissue in primary hyperplasia is carried out on the same principle as subtotal thyroidec-

tomy for the hyperplasia of hyperthyroidism. There are also indications for subtotal resection of an adenoma, one of which also calls for less radical resection of primary hyperplastic tissue. A human being cannot survive total absence of parathyroid tissue with any comfort or safety in spite of the administration of the recently introduced A. T. 10. The indications for subtotal resection have been given in a previous article¹, a new emphasis is given in the present review.

If a patient has had a previous parathyroid exploration and one or more normal glands have been removed, subtotal resection of an adenoma is indicated unless viable, uninvolved parathyroid tissue is definitely seen. Subtotal resection may be indicated, if a previous search has been made, even though no normal tissue was known to have been removed. If at the secondary operation dense scar tissue is found in the region where normal glands are most likely to occur, it is safer to assume that the uninvolved parathyroids have been damaged either by direct trauma or loss of blood supply. If pieces of tissue were cut out for examination, or particularly if a subtotal thyroidectomy was done in the hope of finding parathyroid tissue within the thyroid substance, a subtotal resection should be weighed.

Subtotal resection of an adenoma or less radical subtotal resection of primary hyperplasia is indicated if tetany of the recalcification period is anticipated. In patients with extensive bone disease, secondary to hyperparathyroidism, severe low calcium tetany may follow correction of the primary disease. This tetany is due to the rapid absorption of calcium by the bones. Preoperatively, it may be predicted if the phosphatase of the serum is ten Bodansky units or greater.

The nature of this tetany of the recalcification period is not completely understood. The disordered metabolism resulting in the decrease of blood calcium is different from that in hypoparathyroidism. First, the serum phosphorus level is low instead of high. Already low due to the hyperparathyroidism, it descends further during the 48 hours after operation, rising to the low preoperative level in the course of the first postoperative week, and to normal as recalcification is completed. Second, the phosphatase, already elevated, rises precipitously after operation (during the first 48 hours there may be a transient fall). As the skeleton recalcifies, the phosphatase falls gradually to normal. In patients with severely depleted bones, this process may require more than a year in spite of a huge daily intake of calcium and phosphorus. During this long period, tetany remains latent.

The phosphatase level of the blood serum is believed to be proportionate to the number of osteoblastic cells ready to form bone. In the presence of an excess of parathyroid hormone, these cells are unable to work to capacity. The change in parathyroid function following resection of an adenoma apparently releases them much as a trigger fires a gun. Their rapid absorption of calcium results in the tetany. It may be that subtotal resection is not the best method of slowing up the discharge of this tetanic gun.

The possible occurrence of carcinoma in the remnant of the parathyroid

adenoma might be considered as a contra-indication to subtotal resection. In only one of our nine cases in which a subtotal resection of an adenoma has been done, have we had to remove the remnant for residual hyperparathyroidism. In none of the 58 adenomata seen at this hospital has there been any microscopic evidence of malignant degeneration. The report¹³ of carcinoma in a gland giving rise to hyperparathyroidism is not beyond question. Carcinoma of the parathyroid is a rare disease, in the cases reported no hyperfunction is proven. The possibility of eventual carcinoma should not rule out subtotal resection when life-endangering tetany threatens.

ILLUSTRATIVE CASE HISTORIES

The following case revealed a parathyroid adenoma in the anterior mediastinum, impossible to reach by fingers introduced through a collar incision in the neck.

Case 50—*Mediastinal Adenoma Beyond Reach from the Neck*. A woman, age 26, was treated in a hospital in Hartford, Conn., two years before entry. First, a calculus was removed from the right ureter, then the left kidney was removed because of stones and infection. Following this, a diagnosis of hyperparathyroidism was made on the basis of the blood findings. Exploration of the neck and thyroid regions disclosed three enlarged glands, felt to be consistent with hypertrophy. Specimens were removed for biopsy, normal parathyroid glands were reported. The metabolic signs of hyperparathyroidism continued and the patient was referred to this hospital.

Intravenous pyelograms pictured calcification in the right kidney and slight hydronephrosis. There was no demonstrable bone disease roentgenologically. There was hypercalciuria, a blood calcium level of 13.6 mg, phosphorus of 2.4 mg, phosphatase of 4.2 units.

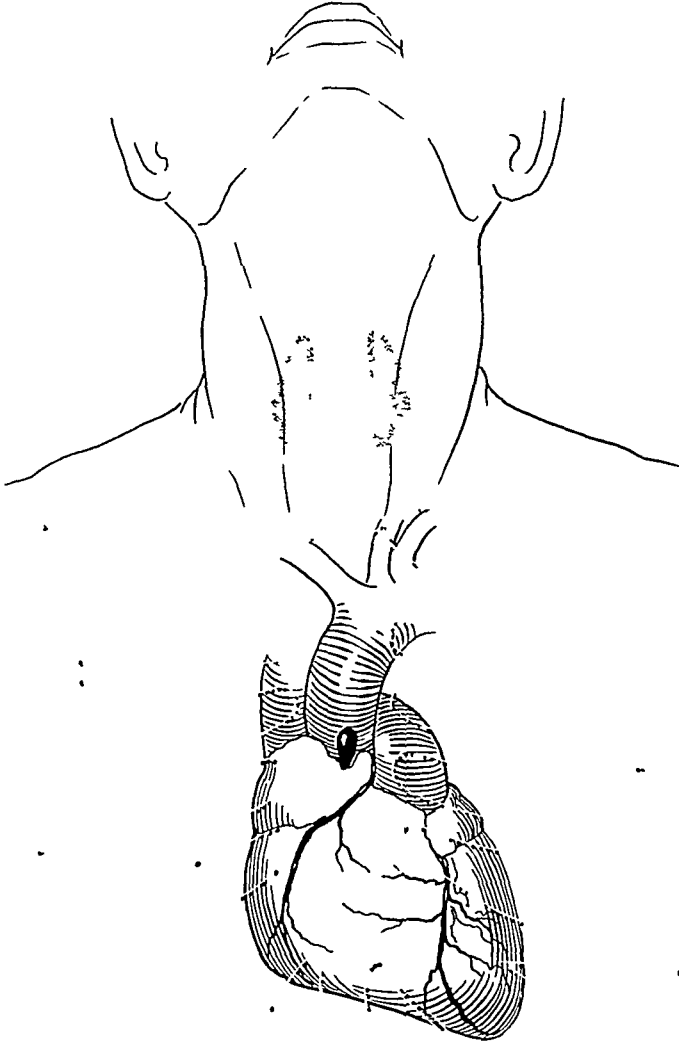
Operation—Because of the gross diagnosis of hypertrophy made at the previous operation, the neck was reexplored. The thyroid region was searched. A remnant of one of the glands previously exposed was identified, a specimen removed for biopsy, and reported normal. Because of its nodular character, the left thyroid lobe was subtotally resected, sectioned at the operating table, but no parathyroid tissue was found. The entire neck region and posterior mediastinum were explored. Then the anterior mediastinum was entered by blunt finger dissection. A normal thymus gland was identified and the upper portion was teased out, no parathyroid tissue was found in it and none had been felt near it. Tissue could be felt in the anterior mediastinum at the tip of the finger, and it was realized that more thymus was left in the chest.

During such a blunt, blind search in the anterior mediastinum there is inevitably considerable motion of air in and out of the chest, and its occurrence at this operation failed to cause concern. The patient died two hours after operation of a bilateral partial pneumothorax. By the blunt dissection, small openings had been torn into the pleural cavities. Postmortem examination confirmed the presence of further thymus tissue lying in front of the ascending aorta, and at the very bottom, poking its nose out of the thymic capsule, lay the parathyroid adenoma. The adenoma lay just in front of the upper portion of the right auricle, between the upper anterior pericardium and the sternum. It was fully two inches below the reach of fingers inserted at the notch of the manubrium (Fig. 11).

COMMENT—This parathyroid adenoma was in the lowest position of any we have found, and lower than any parathyroid gland we have seen reported in the literature. The experience with this patient demonstrates not only the danger of blunt and blind dissection in the chest but also that parathyroids

may be beyond reach, it has been responsible for our considered return to direct exploration of the anterior mediastinum through a divided sternum.

The following case illustrates the wisdom of exploring the anterior mediastinum under direct vision. The adenoma was not felt although touched by fingers inserted from the incision in the neck. Its position was not disclosed until the second-stage operation.



*Manuel
M. Letiche
-1941-*

FIG. 11.—Position of parathyroid adenoma found at autopsy in Case 50. The adenoma lay at the lower end of the thymus within the thymic capsule and was a good two inches beyond the reach of fingers introduced through the neck incision.

Case 55—*Futility of Blind Exploration of Anterior Mediastinum* A woman, age 54, eight years before entry underwent a pelvic repair operation. A backache which was unrelieved by the operation was later diagnosed sacro-iliac arthritis. Four years later, during a gastro-intestinal series, kidney stones were discovered, and after another year one kidney "full of stones" was removed. It was not until 18 months before entry, when she was studied for various skeletal aches, that hyperparathyroidism was diagnosed. A parathyroid exploration was undertaken in New York, N. Y. The neck region was explored but only one parathyroid, presumably a normal one "at the right lower pole of the thyroid," was disclosed. Because of increasing skeletal pains and continued hypercalcinuria, the patient was referred to this hospital.

Mild generalized decalcification was demonstrated. The blood serum calcium averaged 15.5 mg, the phosphorus 2.1 mg, and the phosphatase 7 units. There was a high concentration of calcium in the urine.

Operation—Since the surgeon had been able to expose only one possible parathyroid gland at the previous operation, reexploration of the neck was indicated.

First Stage—November 23, 1940. The areas covered at the previous operation were clearly delineated by dense scar tissue, a complete exploration of neck and posterior mediastinum was accomplished and no parathyroid adenoma was found. In an effort to avoid a third operation the anterior portion of the superior mediastinum was explored blindly with fingers, no tumor was felt.

Second Stage—December 5, 1940. After division of the sternum, a long, thin thymic remnant was easily identified. It was dissected upwards to within 1 cm of the left innominate, where dense tissue reaction from the recent blind exploration was encountered. No parathyroid tissue was seen within the free portion of the thymus. Other portions of the mediastinum were, therefore, explored. When no tumor was found the scarred area was returned to as last resort. As the thymus was followed up into the area where fingers had felt before, a parathyroid adenoma, measuring 1.8 x 0.8 x 0.5 cm and weighing 0.4 Gm, was found within the thymic capsule, lying behind the inferior margin of the left innominate vein. Figures 8 through 10 are photographs taken at the operation of this patient.

Removal of the entire adenoma has resulted in prompt relief of the patient's symptoms.

COMMENT—The adenoma was undoubtedly touched at the first-stage operation. Although of moderate size, it was not felt as a distinct body because of its soft character and its inclusion within a tissue of nearly the same consistency and its position near a large collapsible vein. By yielding to temptation at the first stage the second was made much harder.

In the following case, the thymus gland served as a guide to the prompt discovery of a parathyroid adenoma embedded in the scar tissue of the previous explorations.

Case 57—*Area of Exploration Defined by Thymus* A woman, age 30, noticed the onset of bone pains seven years ago. During the course of these years the pains spread to her whole body and the severity increased. During the last eight months she was bedridden.

Three and one-half years ago, at two operations in a hospital in New Haven, Conn., epulis tumors were removed. Three years ago, in a second New Haven hospital, the diagnosis of hyperparathyroidism was made. Two parathyroid explorations were performed. At the first, the neck was explored and "a parathyroid at the anterior surface of the upper pole was identified and removed", pathologic section showed it to be a lymph node. At the second, the sternum was divided with rongeurs and the anterior mediastinum explored, no parathyroid tumor was found.

Two years ago, in a third New Haven hospital, a second exploration of the neck was made, subtotal thyroidectomy failed to reveal any parathyroid tissue. Six months ago, at a hospital in Boston, Mass., a third exploration of the neck was made, the available portions of the mediastinum were searched. After this fourth unsuccessful operation, roentgenotherapy was administered to neck and mediastinum.

Because the disease had progressed relentlessly, she was referred to the Massachusetts General Hospital. The skeleton showed an extreme degree of involvement with several huge giant cell tumors. The left ureter was blocked by a large stone. She had a severe anemia, in spite of a 4 per cent reticulocyte count. Her blood volume was increased 35 per cent above normal. The blood calcium was 14.5 mg and phosphorus 2.2 mg.

Operation—Second Stage Because of the three previous attempts we excluded generalized hyperplasia and thought the existence of a tumor in the neck or posterior mediastinum unlikely. An adenoma was presumably to be found in the anterior mediastinum lower than the area previously searched. It was, therefore, decided to explore first the region of the lower ascending aorta and pericardium. The sternum was divided into both interspaces and the aorta identified. The lower end of clearly defined thymus was exposed, the margins led upward into the scar tissue of the previous operation. Because it was unlikely that parathyroid tissue would exist below thymus, it was decided to follow the thymus through the scar tissue in spite of the previous search. As the thymus was freed upward, a large adenoma was seen lying against the pleura on the left side. The adenoma lay outside the thymus but in close proximity, it was posterior to the plane of the thymus, between pleura and upper ascending aorta. The anterior and medial surfaces were scarred, showing that previous dissection had come near it. The main arterial supply entered the gland near the bottom, coming from vessels along the pleura and lung root. The largest vein emptied upward into the innominate vein.

The adenoma was subtotally resected because of the possible damage produced by the previous explorations and thyroidectomy, and also because of the extensive bone disease. The remnant was swung anteriorly behind the manubrium on the venous pedicle. The thymus gland was left intact.

In this patient, prolonged search was obviated by scrutiny of the neighborhood of the thymus.

Discussion—The first patient in whom a parathyroid adenoma was found in the anterior mediastinum by the direct approach through the sternum was Case 6 of this series. It was this patient's seventh operation seeking the tumor.^{3,4*} One week later, in another patient, we removed a parathyroid adenoma from a similar position by teasing it out with fingers introduced through the neck incision. Both tumors lay opposite the second intercostal space, and in retrospect it was believed that the first tumor could have been pulled out by the same procedure had its position been accurately known. Since then, two more tumors hidden from view have been fished out of the anterior mediastinum, and in the last publication on the surgical problem from this hospital⁴ it was stated that "splitting of the sternum to afford a direct visual approach to the anterior mediastinum is a procedure that will rarely be required."

Since publication of this article, experience has modified this point of view. First, a patient, not included in the series of proven cases suspected

* Gordon-Taylor and Handley¹¹ have also reported the removal of a parathyroid tumor by a transsternal approach.

of having a mild degree of hyperparathyroidism was operated upon. The entire neck and posterior mediastinal regions were explored, three asymmetrically placed normal parathyroids, but no adenoma, were isolated. The anterior mediastinum was searched by palpation with fingers. Nothing further was found and the fallacy of this blind procedure was then appreciated. If this patient indeed had the disease, the tumor would have been small and, therefore, not palpable.*

In addition, there are the two patients mentioned above under Multiple Adenomata (page 721) who presumably have a second adenoma (mild hyperparathyroidism remains following the removal of the one adenoma), and who have had their anterior mediastinum explored digitally†. Finally, there is Case 50, with the adenoma which was totally inaccessible. With this one definite and three probable failures (to recover a parathyroid tumor from the anterior mediastinum *via* the neck incision) to our debit, a reevaluation of the sternal-splitting operation was imperative.

The direct approach to the anterior mediastinum has now been employed on five patients. The adenomata of three of the nine patients with previous unsuccessful operations were found by this approach, in only one of these, Case 57, did we proceed directly to the thorax without first reexploring the neck. In the fourth patient, Case 54, the use of the second-stage followed the first-stage as outlined in this paper.

The fifth time the anterior mediastinum has been explored through a divided sternum was in a boy, age 14, in whom hyperparathyroidism was excluded by operation. Acute atrophy of bone had simulated hyperparathyroidism. His case is reported elsewhere¹⁵.

The illegitimate employment of the sternal-splitting operation will raise the operative mortality of hyperparathyroidism. The complications of opening the thorax are greater than those of exploring the neck but not greater than those of attempting to explore the thorax from the neck. If the anterior mediastinum must be explored, it is as safe to do so directly at a second operation, and this operation will be successful. The only way to prevent the increase in the mortality rate of the surgery of hyperparathyroidism is to make certain by an adequate first-stage operation (neck and posterior mediastinum) that the second-stage (anterior mediastinum) is essential.

SUMMARY

The problem of the surgery of hyperparathyroidism resolves itself into training of the eye, understanding the abnormal physiology of parathyroid glands and recognition of their widespread distribution.

* Since no further ureteral stones have appeared and the metabolic changes remain questionably abnormal, direct exploration of the anterior mediastinum has not been advised and the nature of this patient's fourth gland is not known.

† One of the two patients, Case 11, had developed carcinoma of the thyroid between the primary and secondary operations. The other, Case 40, has had to undergo a gastrectomy since his parathyroid operation. Exploration of his anterior mediastinum is contemplated.

The incidence of enlarged parathyroid glands in the mediastinum in 60 proven cases, from the Massachusetts General Hospital, is reported

The difficulties in discovering these glands in the anterior mediastinum are reviewed, blind dissection with fingers is uncertain and as hazardous as the direct approach by splitting the sternum

The operative plan as employed at present at this hospital is described in detail. The search is divided into two stages. In the first, the neck and posterior mediastinum are explored. In the second, the anterior mediastinum is opened to dissection under direct visual control by splitting the sternum. This second-stage must be reserved until after an adequate first-stage operation.

The large number of cases of hyperparathyroidism diagnosed at the Massachusetts General Hospital speaks for the tradition of metabolic research of our medical colleagues. The success in proving the diagnosis and benefiting the patient is a result of the versatility of Dr. Edward D. Churchill's surgical point of view. The author is indebted to him not only for sharing the operative assignment of parathyroid disease but also for his criticism.

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DISCUSSION—DR FRANK H LAHEY (Boston, Mass) I wrote to the authors, when they invited me to discuss this paper, that I would only accept the invitation with the statement that I had not had a large experience with this problem On the other hand, we have dealt with some of these intrathoracic parathyroid adenomata It is an interesting subject It is one that needs frequent discussion, and it is particularly interesting to hear this paper from the Massachusetts General Hospital, where so much pioneer work has been done on this subject

I am sure that Doctor Cope will not feel offended if I reiterate what he has already said, that this represents the combined efforts of the medical men at the Massachusetts General Hospital, who have been interested in metabolic disease there, and the surgeons, and all of us who have anything to do with hyperparathyroidism must feel a deep sense of obligation to the men in the Massachusetts General Hospital who have done this work They have done the pioneer work in this country to establish this disease on a sound basis

Figure 1 shows a patient with an intrathoracic parathyroid adenoma which I removed, and demonstrates the degree of chest collapse and round back which can develop in these large parathyroid adenomata It is interesting that Doctor Cope and his group have demonstrated the relationship of the intensity of the disease to the size of the tumor Figure 2 is a roentgenogram of this patient, with shadows marked out, the lower shadow being the arch of the aorta, and the upper shadow the adenoma in the mediastinum Note the amount of vertebral body collapse Figure 3 shows about two-thirds of the tumor removed from the mediastinum

On the other hand, Figure 4 is a roentgenogram showing a mediastinal adenoma which has become cystic, which probably never produced any symptoms That was removed last year, without difficulty, from the mediastinum

So we have at least the problem that we can have some of these adenomata not producing the degree of decalcification that goes with the usual case

One of the problems with which we have had to deal is the intrathyroid parathyroid adenoma We have found three intrathyroid parathyroid adenomata and, as the author



FIG 1



FIG 2

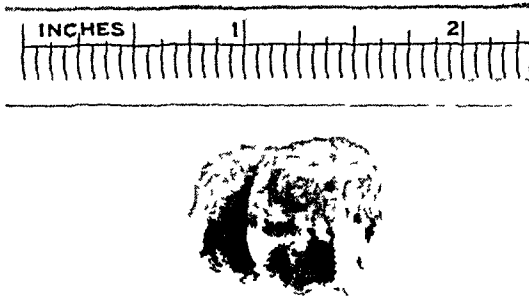


FIG 3

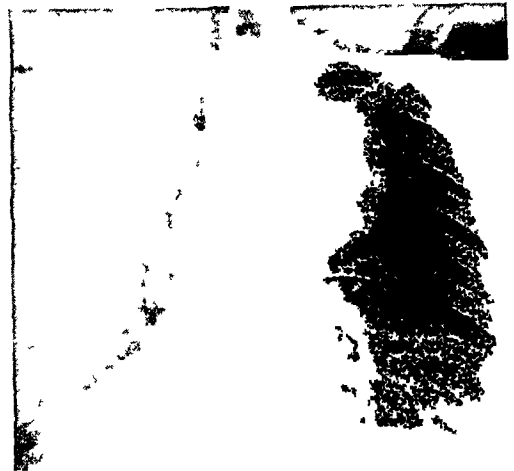


FIG 4

states in his paper, the parathyroid adenoma which is apt to be intrathyroid due to the fact that it rests against the side of the larynx, where the upper lobe presses on the larynx, is the superior parathyroid

Now, I would like to say just a few words for those general surgeons who do not deal with these cases in large numbers. In the paper, there is stressed the fact that there should not be removal of normal parathyroids. We have had to operate on some of these, in which two of the parathyroids have been removed, and so it presents a very serious problem. One should learn, in dealing with thyroids, what normal parathyroids look like. Since we have transplanted 300 microscopically proven parathyroids in the course of thyroidectomies, we have acquired a considerable knowledge of at least the normal location and the appearance of normal parathyroids.

The successful demonstration of parathyroid adenomata will have to do with good exposure, dry fields, good lights, experience with what a normal parathyroid looks like, and mobilization of the thyroid gland. You must, if you look for these parathyroids, tie all the venous connections of the parathyroid gland, which are to the internal jugular. You must then elevate the thyroid gland out of its bed, ligate the superior thyroid

vessels, and detach the upper pole from the larynx, so the gland is adherent only by its attachment to the trachea. You must palpate through-and-through, and, following this, you must, at a later date, in all probability expose the mediastinum. We have exposed the mediastinum in three cases. A very satisfactory way, after splitting the sternum, is to insert the right-angle retractor in the split mediastinum, and then turn it into the longitudinal position, which spreads the manubrium, so the mediastinum is exposed.

I cannot close this discussion without saying what an excellent paper this is. I have read it over thoroughly, and I said to the author that no 15-minute presentation of this paper could do it justice. When you read it, I think you will all agree that it will play a very great part in later making easier for all of us the discovery of some of these adenomata of the parathyroid which, up to now, have been overlooked.

DR EDWARD D. CHURCHILL (Boston) In the natural eagerness to find the parathyroid tumor, the importance of identification of the normal glands must not be forgotten. To put the matter simply, don't go afield looking for a lost sheep until you have counted the ones that are safe in the fold. As soon as the presence of a large prolonged search directed toward finding normal parathyroids. Carefully observe and record the positions of the normal glands. Then, by exclusion, it may be possible to go directly to the site of the missing parathyroid adenoma.

DR OLIVER COPE (Boston, closing) I might emphasize just one point—a distinction should be drawn between a normal gland and an uninvolved gland in a person who has hyperparathyroidism due to adenoma. Doctor Churchill has called attention to the advisability of identifying normal glands. One of the reasons it has been hard to find so-called "normal glands" when looking for an adenoma, is that due to atrophy of disuse they have lost their normal color and are smaller. These atrophic, uninvolved glands are more difficult to distinguish than the normal glands encountered during the course of a thyroidectomy.

OBSERVATIONS ON INTRATHORACIC NEOPLASMS*

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INTRATHORACIC NEOPLASMS are great dissimulators. Whereas, their usual symptoms are cough, sputum that may be blood-tinged, dyspnea and pain, a surprisingly large proportion of patients with intrathoracic neoplasms present a combination of symptoms, physical signs, and even roentgenographic shadows that initially suggests virtually any of the commonplace diseases of the chest. I have recently seen patients with bronchogenic carcinoma who were variously treated for pulmonary tuberculosis, cardiac disease with pulmonary embolism, asthma, chronic bronchitis, pulmonary abscess and delayed resolution of pneumonia for from one to 16 months before the true diagnosis was suspected and made. A patient with a primary sarcoma of the lung, which was first observed as a silent circumscribed shadow, was advised by a well-known internist to have a check-up roentgenologic examination in from three to six months, at four months the shadow had not increased in size and a later roentgenogram was advised, the patient had this made one year later, at which time the tumor filled nearly three-quarters of his hemithorax (Fig 3). A patient with an intrathoracic spindle cell sarcoma, that overlapped the left border of the heart, was treated by a heart specialist with digitalis for 13 months for cardiac enlargement and a murmur that suggested mitral stenosis. A patient I have recently seen with a neurofibroma was treated for diaphragmatic hernia for six months, and another was treated for scoliosis with low back pain for 15 months. Many of the tragic consequences that such mistakes entail may be avoided by a critical examination of some of the diagnostic errors that are likely to lead to mistaken diagnoses. Space will not, however, permit a complete discussion of those nonneoplastic lesions that may be mistaken for neoplasms.

In the present communication, I shall present chiefly those personal observations on intrathoracic neoplasms that have been made by my colleague, Cameron Haight, and myself, during a period of many years. Many of the statements I shall make, and advice I shall offer, are based on lessons we have learned from diagnostic and other errors we have made in meeting situations for the first time that have not been adequately described by others or that have been only incidentally mentioned in case reports. I shall not undertake, at this time, to present a systematic discussion of the diagnostic and technical surgical phases of the subject, as they have been well presented in the recent excellent monograph of Heuer and Andrus, in the text-books of Graham, Singer and Ballou, Sauerbruch, and Lilienthal, and in the articles

* Read before the American Surgical Association, White Sulphur Springs, W. Va., April 28, 1941.

of Harrington, Denk, and many others. I shall, in short, present here chiefly those observations that seem to me of great practical importance and that have not been discussed or sufficiently emphasized in previous publications.

An ordinary cold, influenza, pneumonia, bronchiectasis, or pulmonary abscess is often the first condition to attract attention to a thoracic illness in cases of neoplasm. Pressure upon the bronchi and lung by an intrapulmonary or extrapulmonary tumor in some way probably initiates the pulmonary infection in many cases. The error in failing to diagnose a neoplasm with reasonable promptness in such cases arises when the persistence of a customarily self-limited infection, or atypical developments in chronic infections, do not arouse sufficient suspicion to cause the physician to investigate the case further. The occurrence, the persistence or the aggravation of pain, dyspnea, or cough is especially suspicious of neoplasm in such cases.

Tuberculosis and asthma are frequently, and whooping cough is occasionally, mistakenly diagnosed in cases of intrathoracic neoplasm. Cough, blood-streaked sputum, fever, night sweats, fatigue, and pleural pain suggest tuberculosis, and the roentgenographic appearance of some cases of bronchogenic carcinoma may resemble atypical forms of tuberculosis, but the persistent absence of tubercle bacilli from the sputum should arouse a suspicion of tumor. The paroxysmal coughing that occurs in many cases of neoplasm may be mistaken for whooping cough. The asthmatoïd wheezing caused by intrabronchial growths or by extrabronchial pressure has been diagnosed as true asthma innumerable times. The confusion is promoted by the fact that, like neoplasms, asthma persists and often gradually becomes worse, and by the further fact that adrenalin and certain other drugs that relieve the attacks of asthma may also relieve the asthmatoïd wheezing produced by tumors through reduction in vascular congestion. Furthermore, an eosinophilia may occur with uncomplicated neoplasm.

Although pleural effusion occurs with some neoplasms, an encapsulated effusion or empyema, especially an interlobar one, is often diagnosed as the only lesion when no effusion whatever exists. The chance of a mistaken diagnosis of empyema is increased if the patient has fever, leukocytosis, night sweats, and loss of weight, as he may have with some forms of uncomplicated neoplasm, whether benign or malignant. Although the physical signs may be the same in pleural fluid and neoplasm, the history and roentgenologic findings in a huge majority of cases of neoplasm are sufficiently characteristic to lead to a correct differential diagnosis.

Among the manifestations of cardiocirculatory disease that may be simulated by intrathoracic neoplasms are anginal pain, cardiac murmurs (from direct pressure upon, or rotation of, the heart), abnormal electrocardiogram from direct invasion of the cardiac wall by a malignant neoplasm, apparent cardiac enlargement, palpitation, dyspnea, cyanosis, venous dilatation (usually, however, confined to the supply beds of either the superior or inferior vena cava), apparent enlargement of the liver (from depression by a large intrathoracic tumor), and aneurysm. The differential diagnosis

between an aortic aneurysm and a mediastinal neoplasm is at times very difficult because their roentgenographic shape, size, and position may be identical, because a patient with a neoplasm may happen to have a positive Kahn reaction, and because the fluoroscopic and kymographic determination of whether a mediastinal mass has expansile or only transmitted pulsation may be impossible. I have deliberately explored two such cases, in which the clinical situation was desperate, believing them to be aneurysms (which they were), because there was a small but reasonable chance that a removable

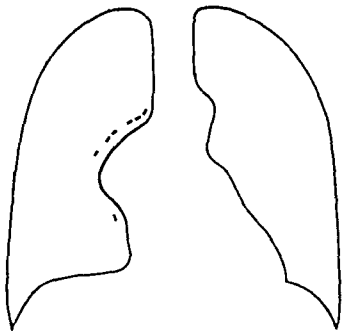


FIG 1 — Fluoroscopically, transmitted pulsation of a tumor may be mistaken for expansile pulsation because the outward thrust of a circular or irregular tumor by transmitted pulsation may create the optical illusion of expansile pulsation

neoplasm might be found. In another case—that of a nonsyphilitic, arteriosclerotic man with a circumscribed nonpulsating tumor lying snugly in the lower left costovertebral gutter—I operated expecting to find a neurofibroma but found an aneurysm instead. On the other hand, I have removed a solid mediastinal neoplasm that was attached to the aortic arch, and which an excellent roentgenologist stated had expansile pulsation (Fig 1).

Arthritis, usually accompanied by hypertrophic pulmonary osteoarthropathy, not rarely occurs early in the course of the thoracic symptoms arising from intrathoracic neoplasms. Willard Van Hazel has recently reported five cases of malignant tumor and two cases of benign tumor in which the sudden onset of arthritic symptoms and joint changes occurred from one month to one year before any thoracic symptoms of the neoplasm appeared. In several of these cases, the arthritic symptoms and signs disappeared within a day or so of the removal of the tumors. While I have seen many cases in which arthritic symptoms and clubbed fingers and toes were apparently a part of the neoplasm syndrome, I have seen only one in which there was sudden relief of the arthritic symptoms following the removal of the tumor, a 1,760 Gm spindle cell myxofibrosarcoma. All the teeth of this patient had been extracted for his presumed arthritis.

Pain in the chest, neck, arms, or abdomen is one of the most valuable of all symptoms in suggesting the possible presence of an intrathoracic neoplasm. Pain may first occur with some form of pulmonary infection and for weeks or months may be intermittent in character. The mistake is frequently made of attributing a progressive thoracic pain to a simple pleurisy, intercostal neuralgia, or spinal arthritis, and of attributing pain in the neck and shoulder region to arthritis or diaphragmatic pleurisy, in the arm to angina pectoris or neuralgia, and in the abdomen to gallbladder disease, gastric or duodenal ulcer, or other abdominal lesion.

When a diagnosis of an intrathoracic neoplasm has been made, the important questions arise as to whether the tumor is benign or malignant and, if malignant, whether it is probably completely removable. An accurate



FIG 2—In 1935 a female, age 54, with hypertension, had an acute upper respiratory infection accompanied by sudden dyspnea cough without sputum and fever for only two days. 1,000 cc of clear, straw colored pleural fluid were aspirated and then the roentgenogram showed a tumor. Top row, left 2 23 35, before aspiration, right, 3 4 35, after aspiration.

During the next five years the patient had fairly good health except for some dyspnea, a sensation of tightness in the chest and several brief attacks of pleurisy. She had no cough sputum or hemoptysis. Roentgenograms in 1937 showed an increase in the growth of the tumor. The posteroanterior and lateral roentgenograms of February, 1940, are reproduced in the middle row. The patient was rejected for surgical treatment by a well known clinic in February, 1940, because of the risk of operation in a patient, age 59, with hypertension, the long duration of the disease, and the few troublesome symptoms.

She was referred to me by Dr R L Pott, of Grand Rapids, in March, 1940. I advised operation because of the danger to the already overworked heart from direct pressure by the increasing size of the tumor, because of the danger of malignancy, and because of the probability of the development of severe pain. After taking a 1200 calory diet for three and a half months, the patient lost 18 pounds and the blood pressure dropped from 210/100 to 170/90.

The tumor which was reported by Dr C V Weller as a rather cellular xanthofibroma with numerous foam cells, not sufficiently cellular to be considered sarcomatous but which might be expected to recur if not completely removed was completely removed on 7 25 40. There was only mild, brief postoperative shock and the patient left the hospital 20 days after operation with a blood pressure of from 120/60 to 142/74, with a pulse of from 80 to 90. For several months her systolic blood pressure was about 130 but when last seen at the end of October 1940, was about 205. The patient then had no complaints except slight dyspnea and tightness in the chest, and was doing light housekeeping without difficulty. The bottom row of roentgenograms were made on 3 5 41, seven months after operation.

preoperative pathologic diagnosis of intrathoracic neoplasms, apart from esophageal carcinomata and those bronchogenic carcinomata that can be biopsied endoscopically, and those neoplasms that have infiltrated the thoracic wall or have metastasized to a site from which a biopsy specimen may be obtained, is virtually impossible. Exception may be taken to this statement on the ground that an exact diagnosis can frequently be made from a needle aspiration biopsy specimen. I advise against aspiration biopsy in any but exceptional circumstances because (1) the preoperative determination of the cell type and of benignancy or malignancy does not determine operability, (2) the introduction of a large needle into a tumor may cause hemorrhage inside or outside it, may cause a cyst to rupture or to spill possibly infected contents, may produce a cerebral embolism or, if the tumor is malignant, may produce an implantation metastasis in the needle track of the thoracic wall, (3) the introduction of a large needle into an intrapulmonary tumor across a pleural cavity that may not have been obliterated by adhesions may cause pyogenic organisms from the lung to infect the pleural cavity, thereby greatly reducing the chance of a successful removal of the tumor.

As many benign neoplasms are potentially malignant and as a reasonably large proportion of malignant tumors can be removed completely, virtually every case of intrathoracic tumor should be promptly explored surgically. (1) If there is no evidence of metastasis or unresectable invasion of the adjacent thoracic wall, (2) if the patient's general condition does not contraindicate the operation, and (3) if the tumor is not a lymphoblastoma. Mediastinal tumors with a circumscribed border are especially difficult to diagnose, lymphoblastoma, dermoid cyst or teratoma, aneurysm, mediastinal abscess, a mass of tuberculous nodes or of carcinomatous nodes of which the primary carcinomatous lesion may not have been discovered, fibroma, lipoma, thymoma, various forms of nonlymphoblastomatous sarcoma, and miscellaneous other neoplasms must be considered. When there is doubt as to the diagnosis, as there frequently is, and when an enlarged lymph node is not available for microscopic examination, the patient should be given a therapeutic test dose of deep roentgenotherapy in order to determine whether the response indicates the probable presence of a lymphoblastoma. I cannot emphasize too strongly that, with rare exceptions which may be disregarded, this is the only proper use of roentgenotherapy as a diagnostic or therapeutic measure in possibly operable thoracic neoplasms. I have seen a number of patients with both intrapulmonary and extrapulmonary malignant neoplasms who lost their lives because they were denied surgery at a time when their tumors were probably completely removable, merely because the tumors had temporarily decreased slightly in size as a result of roentgenotherapy. By these remarks I do not intend, of course, to deny the great palliative, temporary benefit that roentgenotherapy may bestow upon certain patients with inoperable intrathoracic neoplasms.

In the last paragraph, I stated that every intrathoracic neoplasm, with

certain exceptions, should be promptly explored surgically. While it is true that many benign and even some malignant tumors grow very slowly and can be safely removed after a long period of observation, it is equally true that a much larger number of tumor cases suffer seriously or fatally from the delay caused by a period of observation. Increasing experience has shown that many strictly circumscribed intrapulmonary and extrapulmonary tumors, which were formerly generally considered as benign, are malignant. If, therefore, circumscribed tumors are observed for one or more months in an effort to determine whether the rate of growth indicates benignancy or malignancy, the malignant tumors are likely to become inoperable because of metastases. The case shown in Figure 3 illustrates the fallacy of reliance upon rate of growth for the determination of benignancy or malignancy. Recently, I saw in consultation a patient who had had a small, well-circumscribed lesion in the lingular portion of the left lung which increased only slightly in size during an 18-month period of observation, during the last few months of observation an abscess formed in the lesion and obstructive bronchial symptoms finally led to a bronchoscopic diagnosis of carcinoma, which was then inoperable. As neoplasms that are actually benign often unexpectedly become malignant (perhaps after the termination of a period of observation designed to determine benignancy or malignancy), and as benign tumors may slowly or rapidly grow to enormous size, seriously impairing the function of the lungs and mediastinal organs, when the risk of their removal is many times greater than the risk of their removal when small, there is a real danger to life in delaying operation for benign tumors. Furthermore, the degenerating central portions of enlarging benign tumors, or the contents of dermoid or other cysts, may perforate into a bronchus, the tumors thereby becoming secondarily infected and densely adherent to their surroundings. The growth of neurofibromata arising in or near an intervertebral foramen, may proceed into the spinal canal, producing spinal cord paralysis.

If, as I believe, all benign and malignant neoplasms, with certain exceptions, should be promptly explored surgically, it follows that surgical exploration should be carried out for those wholly silent neoplasms that are accidentally discovered in the course of a routine physical examination (Fig. 3). They are as dangerous in the silent stage as in the symptomatic stage. If the tumor should be malignant, metastases may occur while the patient and physician are awaiting the possible occurrence of troublesome symptoms. Surgical removal is the only curative treatment of either benign or malignant neoplasms.

In the preceding paragraphs, emphasis has been placed upon the difficulty or impossibility of determining before operation in many cases whether a tumor is benign or malignant, and upon the importance of prompt operation unless metastasis or invasion of the thoracic wall indicates that the tumor is malignant and irremovable. Obviously, an effort should be made

to determine if such invasion or metastasis has occurred. Careful palpation for an enlarged cervical or axillary lymph node, the microscopic examination of which might show malignancy, has not rarely determined inoperability. The routine examination of the entire body, including the liver, spleen, kidneys, breasts, uterus, prostate, and testicles for possible primary or meta-

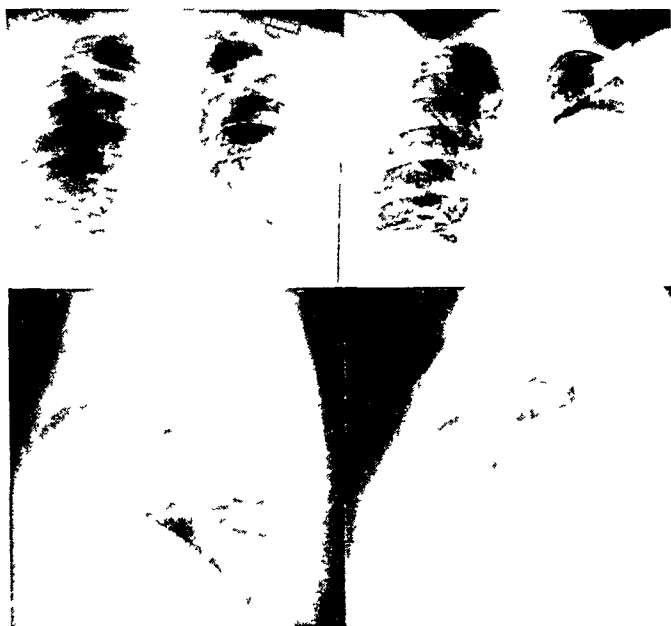


FIG 3.—Primary intrapulmonary sarcoma. The roentgenograms showing the small tumor were made in November, 1939 and the larger tumor in December, 1940 five days before total pneumonectomy. The symptomless tumor was discovered in July, 1939 during a routine physical examination in another clinic where the patient was advised to reduce his excessive weight (223 pounds at time of pneumonectomy) and to have another roentgenologic examination in from three to six months. As the November 1939 (four months later) roentgenograms showed no growth, the patient was advised to have another roentgenologic check up later (which he deferred for a year). In October 1940, a 'cold' was followed by persisting dyspnea, pain and cough with whitish blood streaked sputum. Bronchoscopic biopsy showed a submucosal sarcoma 2 cm distal to the left upper lobe orifice. Thorough examinations revealed no extrathoracic primary neoplasm. Pathologic examination of the removed lung showed an intrapulmonary, encapsulated, soft, gelatinous whitish, spindle cell sarcoma that had characteristics suggesting only local malignancy and an origin from a neurofibroma. Two lymph nodes removed from the surface of the esophagus immediately below the inferior pulmonary vein showed no evidence of metastasis. The patient was discharged from the hospital 46 days after operation in excellent health except for a small residual empyema. Patient referred by Dr. E. T. Sladek, Traverse City, Michigan.

static lesions is obviously important. Even though no renal mass can be felt, a circular, circumscribed intrapulmonary tumor is sufficiently suggestive of a metastasis from an hypernephroma to justify pyelograms.

Malignant erosion of ribs, vertebrae, or sternum, in contradistinction to the thinning of bone by simple pressure, can be determined in some cases only from Potter-Bucky roentgenograms made in suitable projections. Thoracoscopy after the aspiration of pleural fluid and the substitution of air, may reveal the parietal pleural implantation of a malignant tumor that roentgenograms may have failed to disclose, otherwise, thoracoscopy almost never is capable of determining operability or of furnishing information of value that cannot be obtained by other means. As approximately 75 per cent of bronchial neoplasms are visible bronchoscopically, bronchoscopy is not only invaluable in determining the type of the lesion but, more importantly

from the surgical point of view, the exact position of the lesion in the tracheobronchial tree. Bronchoscopy may also furnish information of value in some cases in which the neoplasm has not arisen in the larger bronchi. Pneumoperitoneum is occasionally useful in distinguishing between supra-diaphragmatic and infra-diaphragmatic neoplasms.

The following symptoms and signs are strongly suggestive of a malignant neoplasm and of inoperability: Dysphagia, paralysis of the recurrent laryngeal, or phrenic nerve, Horner's syndrome, hemorrhagic pleural fluid, serous pleural fluid in the presence of a small tumor, dilated veins, a sudden increase in the size of a tumor, severe pain, and rapid loss of weight. None of these symptoms or signs should, however, be accepted as absolute proof of either



FIG. 4—At the time of the left hand roentgenogram (4540) the patient, a male, age 47, was admitted to a well-known tuberculosis sanatorium because of fatigue and bloody, mucoid sputum, of one month's duration but without pain, anemia or loss of weight. Tuberculosis was tentatively diagnosed. During the following four months, nine examinations of the sputum were negative for tubercle bacilli. A malignant neoplasm was promptly suspected but operation was deferred because of two negative bronchoscopic examinations, and in spite of the progressive growth of the lesion as seen in the subsequent roentgenograms of 7940 (middle) and 9140 (right).

Total pneumonectomy, on 92340, revealed medullary squamous cell carcinoma, Grade III, the bronchial origin of which in the right upper lobe bronchus was beyond bronchoscopic vision. Many mediastinal lymph nodes were removed which showed metastases. The patient died, 1241, from cerebral metastases. There is a reasonable presumption that pneumonectomy at the time the first roentgenogram was taken would have cured the patient. Patient referred by Dr. Hillis Seay, Huntersville, N. C.

malignancy or inoperability as all of them have been observed in cases of benign neoplasm. Horner's syndrome may occur with a benign neurofibroma involving the sympathetic chain. The sudden increase in the size of a tumor, while strongly suggesting malignancy, may be due to hemorrhage within a degenerating benign neoplasm or to the rapid increase in the secretions of a cyst, perhaps from infection. Well-circumscribed extrapulmonary neoplasms may be malignant, although most of them are benign. Most circumscribed intrapulmonary neoplasms, however, are malignant bronchogenic carcinomata (Fig. 4). While most neoplasms that are not well-circumscribed are malig-

nant, such neoplasms may be benign, the loss of sharp definition at the edge of the tumor being due to inflammatory changes in the adjacent lung or pleura, or to localized collapse or atelectasis of the adjacent lung

It is apparent from the statements in the last and other paragraphs that, apart from the diagnosis of malignancy from a biopsy of the tumor, or from a demonstrable metastasis, there are no reliable criteria from which the benign or malignant character of an intrathoracic neoplasm can safely be determined. The patient's safety, therefore, depends upon a prompt exploratory operation

SURGICAL CONSIDERATIONS

Preoperative pneumothorax rarely adds information of value except in distinguishing between a pulmonary, as compared with a mediastinal or thoracic wall, origin of a tumor, which information does not alter the indication for operation. The statement has often been made that a preoperative pneumothorax is valuable in accustoming the patient to the conditions that will obtain at the time of operation in that pneumothorax stabilizes the mediastinum and, by shunting a large amount of blood into the lung of the opposite hemithorax, prepares that lung for additional work. I know of no evidence that supports this opinion, and there is good evidence that contradicts it. The wounding of the lung by the pneumothorax needle or the tearing of pleural adhesions and the lung by an increasing pneumothorax might cause a tension pneumothorax, a serous effusion, or an empyema, which might delay, complicate, or prevent the intended operation.

Immediately before operation, the internal saphenous vein at the ankle should be exposed for the introduction of a blunt needle, and 5 per cent glucose or normal saline solution administered, slowly at first. Since the routine administration of intravenous fluids during and after the removal of intrathoracic neoplasms was begun in my clinic, the condition of the patients has been definitely improved, and in a number of unusually difficult and shock-producing operations the continuous instillation of fluids, including blood, has probably been life-saving. The delay occasioned by the introduction of an intravenous needle *after* the actual necessity for fluids has become apparent may be responsible for fatal shock. The vein is exposed for the introduction of a blunt needle because this is more likely to function continuously than would a sharp needle introduced by puncture. An ankle vein is chosen because a needle in an arm vein might be disturbed by the operating team.

For anesthesia, I prefer intratracheal cyclopropane, perhaps with a small dose of avertin, in conjunction with procaine infiltration of the skin in the line of the intended incision, and of the intercostal nerves. Intratracheal anesthesia is valuable when administered by an expert anesthetist, but by no means indispensable. Should difficulty be encountered in the introduction of the tube, sufficient traumatic damage might be done to the throat and

larynx to interfere with easy respiration and expectoration after operation. Traumatic inflammation of the trachea would cause abundant tenacious secretions that might lead to serious complications. Furthermore, the larynx of a small child may not accept a tube with a sufficiently large attached aspirating catheter to permit the adequate aspiration of abundant tenacious secretions from the trachea, with the result that the patient might suffocate during the operation. From ten to 15 degrees of the Trendelenburg position of the operation table should be used in order to promote the drainage of pulmonary secretions toward the trachea and mouth, and in order to prevent the gravitation of mouth secretions to the lungs.

While certain neoplasms of the thoracic wall may properly be removed extrapleurally, virtually every intrathoracic neoplasm should be removed by a transpleural approach. The chief reason for this is that the wide exposure of the tumor that is obtained, in contradistinction to the relatively narrow exposure afforded in the course of an extrapleural operation, adds greatly to the patient's safety because of superior orientation of the mediastinal and other relationships of the tumor and because of the additional room given for the difficult operative manipulations. Furthermore, experience has shown that even a tedious, time-consuming attempt to keep from tearing the parietal pleura is usually unsuccessful. A tiny tear may allow a large amount of air to pass into the pleural cavity and build up dangerous pressure upon the lungs and mediastinum. If infection should occur in an extrapleural space, it would be transmitted to the general pleural cavity through a tiny tear in the parietal pleura. The traumatic serous effusion that forms as a result of the removal of an intrathoracic tumor and that usually requires one or more aspirations, may be removed more readily and safely from the bottom of the pleural cavity (where it collects when a transpleural approach has been used) than from the bed of the tumor (where most of it would collect if an extrapleural approach, without tearing of the pleura, has been used).

The exact site of the incision in the thoracic wall for the best exposure of a tumor is a matter of major importance. Many surgeons prefer an anterior incision for tumors that are in the anterior part of the chest. In spite of the apparent reasonableness of this choice and the fact that the skin incision may be concealed beneath a woman's breast, I greatly prefer a long posterolateral incision for almost all anterior intrathoracic tumors, for the following reasons: (1) The wider field of exposure affords better orientation and more room for the operative manipulations, especially in the mediastinum posterior to the tumor, and gives an almost equally good exposure anterior to the tumor. (2) The posterolateral approach gives splendid access to tumors in the dome of the thorax, whereas an anterior approach gives poor access because of the intervention of the clavicle and subclavian vessels crossing the first rib. In certain cases, however, in which a tumor is invading the anterior thoracic wall, an anterior incision is preferable to a posterior incision and, in rare cases, a sternum-splitting incision for a combined extra-

pleural-mediastinal and cervical operation is best (3) The postoperative stability of a posterolateral incision is greater than that of an anterior incision

When the posterolateral approach has been chosen, a study of cases illustrated in the literature shows that in a surprisingly large percentage of them the wrong rib has been resected for the best exposure of the particular tumor. As a result, one or more additional ribs have needed to be resected or divided in order to obtain adequate exposure of the tumor, thereby weakening the thoracic wall during the important postoperative period. In a con-

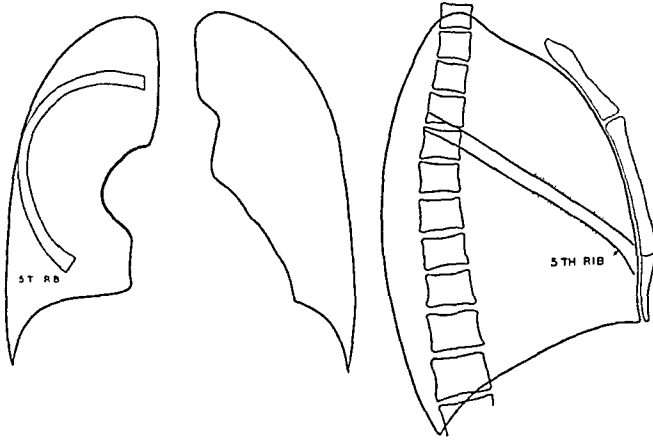


FIG 5—When access to an extrapulmonary tumor in the anterior two-thirds of the chest is gained through the resection of the posterolateral portion of a rib the error is often made of resecting that rib whose posterior portion overlies the center of the tumor in the posteroanterior roentgenogram. In the case illustrated in the diagrams this rib would be the eighth which would be far too low. As the widest working space is approximately between the posterior and anterior axillary lines, the fifth rib should be removed for the best exposure of this tumor.

siderable number of reported cases, four or five ribs have been resected or divided for small or medium-sized tumors for which the resection of a single rib to the midaxillary or anterior axillary line should have been sufficient. In the case of tumors situated in the middle or anterior third of the chest, the common mistake is made of choosing for resection that rib whose posterior end overlies the center of the tumor in the postero-anterior roentgenogram, the removal of the posterolateral portion of this rib places the surgical working space far too low in relation to the tumor (Fig 5).

For tumors that lie in contact with the posterior thoracic wall, a less extensive length of rib should be resected than for tumors in the anterior two-thirds of the chest, this rib should be the one that approximately overlies the upper third and lower two-thirds of the tumor in the postero-anterior roentgenogram. As most tumors lying snugly in the costovertebral gutter cannot be removed satisfactorily after the resection of only one rib, one or more adjacent ribs and intercostal bundles usually need to be divided posteriorly so that, when the ribs have been separated, a triangular opening, with its base posteriorly over the tumor, is formed. The removal of a 2-cm length of a rib close to the tip of the vertebral transverse process and entirely

beneath the sacrospinalis muscle is preferable to the simple division of a rib because the resection of a 2-cm portion prevents the postoperative pain that would occur from the rubbing of the divided ends against one another. Drilling and wiring the rib ends together as a part of the closure of the wound is entirely unnecessary if the 2-cm portion that was resected lies entirely beneath the sacrospinalis and if the incision through the bed of the long length of rib that was resected is firmly closed.

The posterolateral resection of the seventh rib is usually used for a lower-lobe lobectomy, of the sixth rib if both the lower and middle (or lingular portion of the left upper) lobes are to be removed, and of the fifth rib if the entire lung is to be removed. Several surgeons, who have had much experience with total pneumonectomy, prefer the anterior approach, a perimammary incision, splitting of the pectoralis major over the third intercostal space and a parasternal incision of this muscle over the cartilages that are to be divided, a long third intercostal space incision and the division of the third, fourth, and perhaps also the second and fifth costal cartilages. I have used both approaches for total pneumonectomy and greatly prefer the posterolateral approach. Incidentally lobectomy and pneumonectomy, as well as the removal of extrapulmonary neoplasms, whether by the posterolateral or anterior approach, may be carried out through an intercostal incision with or without the division of one or more ribs or cartilages, but without the resection of any rib. The incision through the thoracic wall is, however, facilitated by the resection of a rib, which later regenerates from the periosteum.

The rapid opening of the rib spreader often causes a reflex stoppage of respiration for a few moments. The spreader should be temporarily relaxed until normal breathing has reestablished itself, and then gradually reopened.

The preponderance of opinion among thoracic surgeons is that both intrapulmonary and extrapulmonary neoplasms should be removed in one stage when feasible.

If encapsulated extrapulmonary tumors are approached from within the pleural cavity, the parietal pleura and any subjacent "false capsule" tissue should be incised over the tumor and the dissection carried out in the extracapsular tissue plane. Since the chance of complete removal of a densely

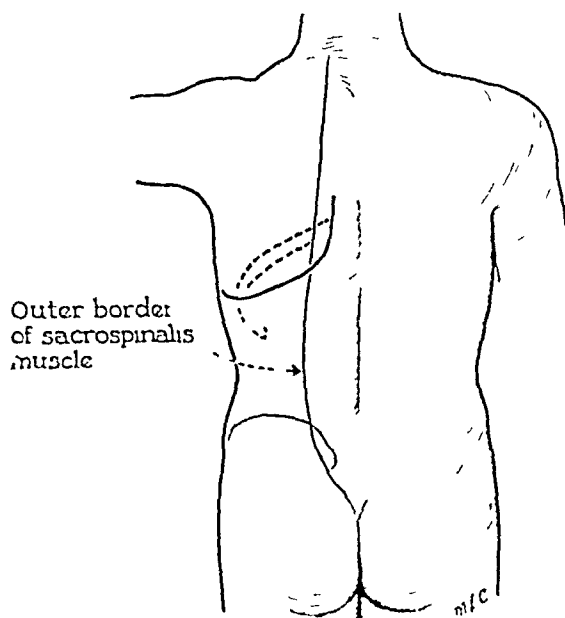


FIG. 6.—Imbrication of the incised layers of the thoracic wall. The vertical part of the incision in the skin and extracostal muscles is made over the sacrospinalis muscle and the horizontal part below the portion of rib to be resected (shaded portion). Imbrication may prove useful in preventing the sucking of air into the pleural cavity with resulting infection should the incision heal imperfectly.

adherent cyst wall is enhanced when the dissection is carried out upon an intact cyst, every effort should be made not to rupture the cyst. Likewise, care should be taken not to tear the capsule that sometimes occurs around soft, friable, extrapulmonary malignant neoplasms since further operative manipulations in the presence of a tear of the capsule are likely to cause successive parts of the tumor to break away, with sharp accompanying hemorrhage that can be checked only by pressure.

A broad surface of the lung is often diffusely and rather firmly adherent to large extrapulmonary tumors. Separation can usually be effected by gentle finger dissection, with the occasional use of sharp division of tough adhesions that might cause more or less deep tears of the lung, if an attempt were made to rupture them with a finger. The profuse brief momentary hemorrhage that often occurs is best controlled by the temporary snug packing of the cleft between the lung and the tumor with dry gauze. Persisting bleeding points on the raw surface of the lung require ligation, and areas of injured alveoli and bronchioles from which air continues to leak should be oversewn with fine catgut. Heuer and Andrus recommend the resection of a "lappet of lung" that might be torn by the primary separation of its adhesions to the tumor. Such a resection would obviously be obligatory if the tumor were actually invading the pulmonary tissue.

Most extrapulmonary tumors receive their blood supply at scattered points on their circumference, rarely (except in the case of neurofibromata arising from an intercostal nerve or the sympathetic chain) can the surgeon discover a single well-defined pedicle. Numerous thick bands of tissue connecting the capsule and mediastinal or other tissues may, however, require ligation. Heuer and Andrus recommend the placing of a Shenstone lobectomy tourniquet around the site of origin of a tumor, especially one at the apex of the thorax, in case the tumor fills the operative field and thereby prevents the checking of hemorrhage and the guarding of important mediastinal structures under vision. It is apparent that the surgeon would need to satisfy himself that the tourniquet did not include any important mediastinal structure.

Since there is evidence to indicate that stimulation of the vagus or sympathetic nerve chain in the mediastinum may cause cardiac or respiratory stoppage, and since several actual cases of such stoppage have been reported as presumably due to the accidental operative stimulation of one or the other of these nerves, I recommend that they be directly injected with 1 per cent procaine solution through a fine needle, if the surgical situation requires that they be disturbed by dissection or if circumstances should require that they be divided. Obviously, the vagus nerve should be injected inferior to its recurrent laryngeal branch.

At intervals of from five to 15 minutes during intrathoracic operations, the lungs should be partly inflated by a moderate increase of the pressure in the gas anesthesia apparatus in order to overcome a tendency toward a

persisting atelectasis and impaired pulmonary circulation from prolonged pulmonary collapse. Such intermittent inflation is especially important when the lung on the side not being operated upon is partially collapsed by a great displacement of the mediastinum.

Patients requiring total pneumonectomy or lobectomy for carcinoma or other neoplastic lesion of the lung may have broad areas of exceptionally dense adhesions between the visceral and parietal pleurae that cannot be safely divided by the customary alternating blunt and sharp dissection. When such areas of dense adhesion represent an inflammatory reaction and not a neoplastic invasion of the thoracic wall, the simplest method for the separation of the lung from the thoracic wall is the incision of the parietal pleura around the area of dense adhesion, followed by the extrapleural separation of the lung and its overlying adherent pleurae from the costal periosteum and intercostal muscles by finger dissection. In such cases, the line of cleavage in the extrapleural tissues can often be readily developed. The leaving of a raw patch of thoracic wall, uncovered by parietal pleura, has no deleterious effect upon the patient's postoperative course. In principle, a somewhat similar maneuver may be used when a tumor is densely adherent to the costal periosteum, the periosteum may be incised just beyond the tumor and the densely adherent periosteum and tumor stripped away as a unit from the rib, which, then, is left bare on its inner surface.

An air-tight closure of the incision in the thoracic wall is important, especially with regard to the prevention of sucking of air into the pleural cavity, which would prove to be a serious postoperative complication (Fig. 6). Closure of the long incision in the parietal pleura and in the periosteal bed of the resected rib may be made with continuous or interrupted sutures placed close together, usually after relaxation of the incision with pericostal sutures around the two ribs adjacent to the pleural incision. Only rarely can the pleura and periosteum be sutured air-tight from the lateral edge of the sacrospinalis muscle to the posterior stump of the resected rib. This gap in the air-tight closure of the pleura can, however, be covered air-tight by suturing the lateral edge of the sacrospinalis muscle (which must, therefore, be carefully protected against being torn at the time it is separated from the ribs at the beginning of the operation) to the intercostal muscles and to one of the pericostal sutures.

The lung should not be inflated by the use of highly positive pressure in the intratracheal tube or face mask before closure of the incision because there is evidence that such inflation may rupture pulmonary alveoli. It is important, however, that the lung should be expanded as soon as possible after operation so that it will completely fill the pleural cavity. The reasons for this are (1) That the removal of all the air from the pleural cavity prevents the driving out of this air by coughing into the layers of the thoracic wall, (2) the complete expansion of the lung brings the visceral and parietal pleurae in contact with one another, pleural adhesions then tend to form rapidly,

thereby preventing pleural infection or limiting it if it should occur, (3) complete expansion of the lung improves the cardiorespiratory functional reserve and, therefore, combats any tendency toward dyspnea, anoxemia and cardiocirculatory decompensation. Partial expansion of the lung may be obtained before the completion of the operation by leaving a catheter, attached to suction tubing, in the pleural cavity until just before the last suture that will produce an air-tight closure of the wound is to be tied. Shortly after operation, a bedside roentgenogram, made preferably in the sitting or semisitting position, should be obtained in order to determine if more than a little air remains in the pleural cavity. If it does, it should be removed by needle aspiration by means of "initial pneumothorax technic."

Space does not permit an adequate discussion of the conditions in which immediate tube drainage should be used after the removal of intrathoracic neoplasms. The indications for tube drainage are relatively rare, one of the most important being when any leakage of air from the lung (resulting from injury during the freeing of a tumor from the lung) persists at the time of closure of the thoracic-wall incision. Reliance upon intermittent needle aspiration of reaccumulating air might result in dangerous pressure upon the lung and mediastinum, and in progressive mediastinal and generalized body emphysema. The drainage tube should be removed early—as soon as the roentgenologic and physical findings indicate that leakage of air from the lung has ceased. Gross contamination of the pleural cavity from the spilling of the infectious contents of a tumor or from the opening of an infected lung may make immediate tube drainage advisable. There is, however, an increasing tendency not to drain such cases routinely but to rely upon a thorough lavage of the pleural cavity and the application of sulfanilamide or sulfathiazole crystals if contamination has occurred, and upon the rapid and complete expansion of the lung by needle aspiration of all pleural air immediately after closure of the thoracic wall incision, in order to bring the visceral and parietal pleurae in contact, thereby eliminating the dead space and fostering pleural adhesions that may wall-off pyogenic organisms before infection occurs.

The routine administration of oxygen during the first day or two after the removal of intrathoracic neoplasms is advisable. The patient should be directed to cough and expectorate any secretions that may be in the bronchi at frequent, regular intervals in order to prevent anoxemia, respiratory distress, or pulmonary infection from the accumulation of infectious secretions. Any air that may remain in the pleural cavity after the initial postoperative aspiration as determined by bedside roentgenograms or physical signs, should be aspirated until virtually all the air has been removed. A variable amount of pleural fluid forms for several days after every operation involving either the inner or the outer surface of the pleura. This fluid should be aspirated daily, or every two or three days (depending upon the rapidity of its formation, its amount, and other circumstances) in order to prevent its causing an unnecessary load upon the heart, great vessels, and lung from pressure, and

in order to remove a culture medium that might be used by any pyogenic organisms that had gained access to the pleural cavity

CONCLUSIONS

Dangerous delay in the diagnosis of intrathoracic neoplasms is frequently caused by their mode of onset symptoms, physical signs, and roentgenographic appearance being strikingly similar to those of the more common thoracic diseases. In the interpretation of roentgenograms, a diagnosis of an interlobar effusion or other type of encapsulated effusion, simple atelectasis, tuberculosis bronchiectasis, pulmonary abscess pneumonia, or nonneoplastic enlargement of the hilar or mediastinal lymph nodes is frequently made when the lesion is actually a neoplasm.

The accurate preoperative pathologic diagnosis of intrathoracic neoplasms, apart from esophageal carcinoma and those bronchogenic carcinomata that can be biopsied endoscopically is virtually impossible. In many instances, the surgeon cannot tell before operation whether the tumor is benign or malignant and, if it should be malignant, whether or not it is removable. As certain benign tumors are potentially malignant and as many malignant tumors may be removed completely virtually every case of intrathoracic tumor should be promptly explored surgically if there is no evidence of metastasis or hopeless invasion of the adjacent thoracic walls, and if the patient's general condition permits.

Good results following the removal of intrathoracic neoplasms, both with regard to a low mortality rate and an uncomplicated convalescence, depend greatly upon the observance of certain special preoperative, operative and postoperative principles.

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DISCUSSION—DR STUART W HARRINGTON (Rochester, Minn) I have been greatly interested in Doctor Alexander's excellent presentation of intrathoracic neoplasms and I am pleased that he has emphasized the difficulties that are often encountered in establishing a definite clinical diagnosis in these cases. He has emphasized the importance of instituting surgical treatment early, which I believe is of paramount importance in those cases in which surgery is considered, but I do not believe that surgical intervention should be instituted until a thorough investigation is carried out both clinically and roentgenologically. The most important lesions to be ruled out before surgery is instituted are lymphoblastomata and aneurysms. The clinical manifestations of these tumors are often meager and rarely pathognomonic, although they are always of great value when correlated with the roentgenologic findings in establishing a diagnosis and in determining the type of treatment to be instituted.

The roentgenologic examination plays a most important role not only in the recognition but also in the differential diagnosis of these lesions. Doctor Alexander has pointed out that all of these tumors are potentially malignant, and one of the important factors in their treatment is early surgical intervention before they have undergone malignant change. Such early removal is made possible chiefly because of the roentgenologic recognition of the tumors. As valuable as roentgenograms are in the diagnosis of these lesions, it is not always possible to make a definite diagnosis of the growth even when utilizing all of the roentgenologic methods now employed, and in many instances it is impossible to differentiate between benign and malignant lesions, which emphasizes the importance of surgical intervention without any appreciable time-interval of observation.

Doctor Harrington then demonstrated the value of the lateral roentgenograms in determining not only their importance in aiding in establishing a clinical diagnosis but also in their value in determining methods of approach. The most common tumors in the anterior mediastinum are the teratoid tumors, the most common tumors located in the posterior mediastinum are usually the neurofibromata, and the tumors located in the midportion of the thorax and which are often the most difficult to differentiate roentgenologically, are usually the lymphoblastomata and aneurysms.

DR FRANK B BERRY (New York, N Y) I should like to mention one additional method of differentiation between the aneurysms and the tumors, and that is in the use

of diadrasit intravenously according to the technic of Robbe and Steinberg, which we have found most helpful

I should like to stress, as Doctor Alexander has, the early operation or exploration for these tumors, which sometimes, as we have found, has to be done over the protest of some of our medical colleagues, because it is certainly true that the smaller they are, the safer is the operation and the easier the removal

We recently had an experience with a patient, a girl, age 12, who had a dermoid cyst of the mediastinum. While she was on the medical ward a fluid level suddenly appeared in the cyst indicating a rupture into the lung. Fortunately, the cyst did not become infected and removal was effected without any accident

I should also like to put on record that we have had one case of a diaphragmatic hernia through the foramen of Morgagni, similar to that shown by Doctor Harrington in that it contained only omentum, and it was as much of a surprise to us as it apparently was to him

DR EDWARD D. CHURCHILL (Boston, Mass.) Doctor Alexander's very instructive series of cases was chosen, with great skill, to show the difficult decisions we face in the surgical treatment of intrathoracic neoplasms. He brought out one point that perhaps could be stressed a bit more, and that was that the early or the first symptoms caused by many of these tumors are interpreted as an ordinary unimportant complaint, usually pneumonitis or "pneumonia"

A few years ago, when the battle was raging between advocates of resection of the prostate by one method or another, someone said that Florida was full of elderly gentlemen wearing penile clips. I can say now, with the same exaggeration, that Florida is full of elderly gentlemen with cancer of the lung, who have been sent there for their cough. We see them wending their way back about this time of year, or we see them being referred back north by Florida physicians

The point about roentgenotherapy is an important one. Only if very conclusive evidence exists that the tumor is of the lymphoblastoma series should a preliminary trial with roentgenotherapy be given. I am delighted to see that radiologists are more and more inclined to refuse to give treatment without a pathologic diagnosis

Now about the question of operation. In general, I agree with Doctor Alexander that we must take a stand for a liberal policy of exploration in this type of case. Twenty years ago thoracic surgery was concerned with the mechanical physiology of the thorax—such problems as the difference between an open and a closed pneumothorax, pressure pneumothorax, mediastinal flutter, vital capacity, and differential pressure anesthesia

During this period, even our distinguished president was alarmed about what he called the "Eclipse of Anatomy" by physiology, and gave an address before this association on this topic. The word eclipse, however, was wisely chosen, because no eclipse is ever permanent, and as soon as these questions were settled, the sun came out again. In the past ten years thoracic surgeons have been busy with the essential spade work in anatomy and pathology

Now we are faced with some very difficult physiologic problems of a new type. Many of the patients concerning whom we are called upon to make a decision regarding operation present themselves with a very low margin of respiratory reserve from degenerative cardiorespiratory diseases

We do not have to go back very far in the history of abdominal surgery to come to the time when technical advances applied solely on the basis of an anatomic-pathologic approach to surgery, resulted in catastrophes, particularly in the patients with low margins of safety. Many of these catastrophes can be avoided to-day, by attention to physiologic phenomena, such as alkalosis, acidosis, inorganic salt balance, water balance, and hemo-concentration

The surgeon faced with the type of decision that Doctor Alexander has portrayed, in a patient with a low margin of safety in cardiorespiratory reserve, from age, emphysema, cardiac insufficiency, or chronic pulmonary infection, must, at times, compromise. Not infrequently, he must content himself with the argument. In the case of this particular man, his best chance lies in this not being a malignant tumor, rather than in my being able to do anything effectively about it, if it is

If the scope of thoracic surgery is to be further extended we need now to conduct a more intensive study of the disturbances peculiar to the patient with a low margin of

safety in cardiorespiratory reserve. Many of the same problems that were faced in abdominal surgery will have to be reconsidered and modified for the physiologic functions peculiar to the thorax. Not only problems of adequate oxygenation but of CO₂ excretion, and the effect of CO₂ retention on the inorganic salt metabolism must be taken into account. Until these problems are solved we must, from time to time, be willing to maintain conservative limits both in the extent of operative procedures and even in the advocacy of exploratory thoracotomy.

DR WILLIAM D. ANDRUS (New York, N. Y.) Doctors Alexander, Harrington and Churchill have stressed the variation in the signs which may be associated with the neoplasms within the chest other than those of pulmonary origin. As has been pointed out, careful study and care of these patients, together with modern methods of anesthesia, make operation a relatively safe procedure.

The same criteria have come to hold in dealing with operations upon mediastinal and other intrathoracic neoplasms that apply elsewhere. Adequate exposure is of tremendous importance. It is very much less dangerous to make a much wider opening in the chest in order to be able adequately to deal with the surroundings of a neoplasm than to be crowded for space.

Doctor Alexander has stressed the fact that none of the criteria which have sometimes been held to be characteristic of malignancy are absolutely accurate. The location of the tumor is highly suggestive in many instances, as for example, the anterior and anterior-superior mediastinum in dermoid cysts. However, the location of the tumor is no more accurate in determining the exact diagnosis or its benignancy or malignancy than is the location of the gastric ulcer in determining its possible malignancy. Size is no criterion, for some of the largest tumors may be benign.

I should like to stress the characteristic of one group of tumors which have seemed to us to be of considerable importance, namely, those that have reached a very considerable size without producing pressure symptoms on the mediastinum. Those tumors, while they may be embryonal and, therefore, possibly malignant in character, are in essence benign. I am referring to the so-called fibrolipomata or fibrolipomatous myxomata. We have recently had two cases of this type, one of which weighed 1,800 Gm and yet caused no symptoms. It was picked up casually on roentgenologic examination following, as in many instances occurs, a respiratory attack which seemed to call attention to the tumor.

Another tumor, in a patient weighing about 92 pounds, proved to be a fibrolipomyxoma of a questionable malignancy, and weighed nearly 4,000 Gm, in other words, close to 10 per cent of the patient's weight. This tumor was successfully removed, and the patient has made a satisfactory recovery.

In dealing with these tumors, it can be said that the tumors that can be removed are either benign, or the fact that they are malignant comes somewhat as a surprise after the pathologist has examined them. Every effort should be made to remove these tumors completely, and this is particularly true of the dermoids, where the mortality is very much the lowest, and the cures very much the highest when the tumor is completely removed.

TOTAL THORACIC AND PARTIAL TO TOTAL LUMBAR SYMPATHECTOMY AND CELIAC GANGLIONECTOMY IN THE TREATMENT OF HYPERTENSION^{*}

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RECENT SURGICAL TREATMENT of hypertension has been directed, primarily, toward a sympathetic denervation of the splanchnic area. Several approaches have been employed. Ventral rhizotomy consisting of intraspinal section of the lower six thoracic and first two lumbar anterior spinal nerve roots has been employed in a limited number of patients. Adson, Craig, and Brown¹ report 27 patients, and Heuer² 21 patients treated and studied by him and Page. Both reports show a limited incidence of serious surgical complications, and the procedure appears to have been abandoned. Subdiaphragmatic resection of the splanchnic nerves and part of the celiac ganglia together with resection of the first and second lumbar ganglia has been employed by Adson. Allen and Adson reported its use in a series of over 300 cases, without an operative death. Blood pressure reduction is given as good or fair in 31 per cent, and temporary or poor in 69 per cent of their patients. Supradiaphragmatic extrapleural splanchnicectomy consisting of resection of a long section of the greater splanchnic nerves above the diaphragm together with the tenth, eleventh, and twelfth thoracic ganglia, the intervening sympathetic chain, and the lesser splanchnic nerves, has been employed by Peet in more than 700 patients. Studies of 350 of these patients have been reported by Peet, Woods, and Braden.³ There was a 51.4 per cent significant reduction in blood pressure. They have operated upon many patients with advanced hypertension. Their operative mortality is given as 3.4 per cent.

Celiac ganglionectomy and denervation of the peri-aortic complex of sympathetic nerves and ganglia has been carried out by Cile⁴ in 213 patients. Transdiaphragmatic removal of the lower four thoracic and first, or first and second lumbar sympathetic trunk ganglia together with a long segment of the splanchnic nerve has been performed by Smithwick⁶ in a large series of patients. Emphasis is placed upon the importance of the postoperative postural hypotension achieved.

A review of these reports and of reports of smaller series of similar operations performed by other surgeons gives the impression that although worthwhile improvements have been obtained in some patients, the therapeutic results, as a whole, have left much to be desired. Clinical and symptomatic benefit have been reported much more frequently than blood pressure lowering. A proper evaluation of the effect of any form of therapy in hypertension is always difficult because of the variety of the symptoms encountered and the

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difficulty of establishing a definite control. The value of splanchnic area denervation in hypertension has been extensively debated.

The rôle of the sympathetic nervous system in experimental neurogenic and renal types of hypertension has been reviewed in a previous report.⁷ It has been demonstrated that splanchnic area denervation does not appreciably alter a normal dog's blood pressure, or the hypertensive response to increased intracranial pressure, or the level of the chronic neurogenic hypertension that follows division of the buffer or depressor nerves from the carotid sinuses, heart, and aortic arch. Complete paravertebral sympathectomy in dogs, employing a modification of the technic originally developed by Cannon and his associates⁸ has been demonstrated to lower temporarily a normal dog's blood pressure, to eliminate the hypertension response to increased intracranial pressure, and to lower the blood pressure of neurogenic hypertensive dogs for a time to the vicinity of the normal. These and other experiments suggested that total paravertebral sympathectomy might accomplish more in clinical hypertension than splanchnic area denervation alone, especially if there should be an element of a neurogenic nature in clinical hypertension. The recovery of some degree of central vasomotor control following total sympathectomy in dogs, as previously reported⁹ is incomplete. It does suggest, however, that the vascular alterations achieved by the operation in clinical hypertension might be limited in duration.

Studies related to experimental renal hypertension of the type developed by Goldblatt and his associates¹⁰ have offered little encouragement to sympathetic surgery in clinical hypertension. This renal type of hypertension persists in the experimental animal after total paravertebral sympathectomy.^{11, 12, 13, 14} This observation demonstrates that the vascular bed is under an influence, probably humoral, the action of which is independent of the sympathetic nervous system. If clinical hypertension were primarily renal in nature, the large splanchnic vascular area denervated by operation would also be under the same humoral vasoconstrictor influence.

The possibility of improving the blood supply of the kidney and thus altering the formation of a renal pressor substance has been suggested by Peet.⁴ Clinical studies of renal hemodynamics have, however, failed to show any consistent alteration following splanchnic area denervation in hypertensive patients (Foa, Woods, and Peet,¹⁵ and Corcoran, personal communication).

The mechanism of hypertension in man is probably complex. It is generally accepted that it is mediated by an increase of the peripheral resistance offered by the vascular bed to blood flow. The extent to which processes comparable to experimental renal or experimental neurogenic hypertension may play a rôle in man in increasing the peripheral resistance has not been clearly demonstrated. Grollman, Williams, and Harrison,¹⁶ Page, Helmer, Kohlstaedt, Fouts, Kempf and Corcoran,¹⁷ and others, are developing tissue extracts which they report to be effective in lowering the blood pressure of renal hypertensive dogs and hypertensive patients. If these substances should prove to have specific action against the renal humoral mechanism, their use

in patients would contribute a great deal toward an understanding of the etiology and, possibly, also toward the control of clinical hypertension. Until their availability and ultimate utility are demonstrated, surgical efforts in the treatment of hypertension appear to be justified.

Total paravertebral sympathectomy might accomplish more than splanchnic area denervation in the treatment of hypertension in man especially if, as is stated above, there should be a component of a neurogenic nature in clinical hypertension. A technic has, therefore, been developed for total paravertebral sympathectomy. This procedure has been attempted on 11 patients with varying degrees of success.

Technic—The operation when carried to completion is undertaken in three stages, two thoracic and one abdominal. At each thoracic operation the stellate ganglion and the entire thoracic sympathetic ganglionated chain, the entire length of the splanchnic nerve and its minor branches and the major portion of the celiac ganglion of that side is removed. An effort is also made, but without marked success, to obtain through the diaphragm the first or first and second lumbar ganglia. Figure 1 shows the sympathetic anatomy involved. The third stage, in those instances in which it is employed, consists of a bilateral excision of the remaining portions of the lumbar sympathetic chains down to or including the fifth lumbar ganglion. The operation is of necessity transthoracic and transabdominal. The thoracic stages were performed under ethylene anesthesia, using positive pressure through a face mask, and the abdominal operation under either spinal or ethylene-ether anesthesia. Long alligator forceps, dissectors, hooks and scissors both straight and curved have been devised for dissection of the nerve roots and branches. A special oval-headed, malleable retractor is used for the lungs and a heavy malleable roundheaded retractor with two small hooks at the end for retraction of the diaphragm (Fig. 2).

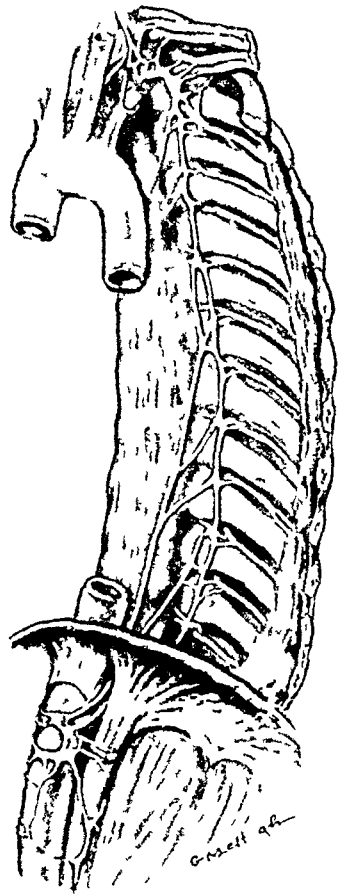


FIG. 1—The relationships of the stellate ganglion, thoracic sympathetic chain, splanchnic nerves, celiac ganglion, and first portion of the lumbar sympathetic trunk. The proximity of the celiac ganglion and the diaphragm is illustrated.

Figure 3 illustrates the location of the incisions. The first incision is made in the axillary region over the third rib which is exposed and resected to the extent of about 12 cm. The thoracic cavity is entered through the rib bed. The lung is retracted, the sympathetic ganglionated trunk is located, and the pleura overlying its upper five segments is divided. Figure 4 represents the exposure

of the upper sympathetic chain and stellate ganglion. The connections of the upper thoracic chain and stellate ganglia are severed. The incision in the pleura is then extended over the sympathetic chain to the level of the eighth thoracic ganglia exposing the beginning of the splanchnic nerve. Figure 5 represents this portion of the exposure. The roots of the ganglionated trunk

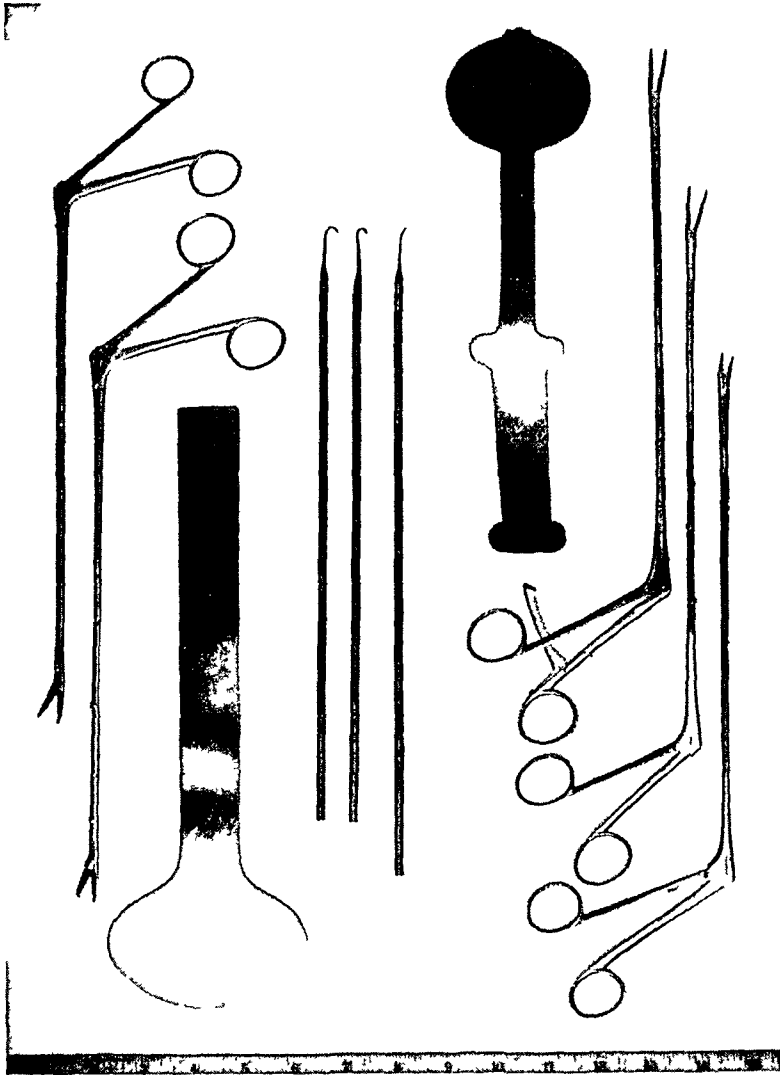


FIG. 2.—The special long alligator forceps, curved and straight scissors, dissector and hooks, oval headed malleable lung retractor, and round headed hooked diaphragm retractor used in the thoracic sympathectomy. The dissector is 12 inches in length.

are cut down to the eighth ganglion, the origin of the splanchnic nerve is freed, and the chain is dropped down into the lower thoracic cavity. The incision in the chest wall is closed.

A second lateral incision is then made over the course of the tenth rib and 12 to 14 cm. of its length is resected. The thoracic cavity is entered through the rib bed. The free end of the sympathetic chain is picked up and its remaining portion and the splanchnic nerve and its connections are dissected.

SYMPATHECTOMY FOR HYPERTENSION

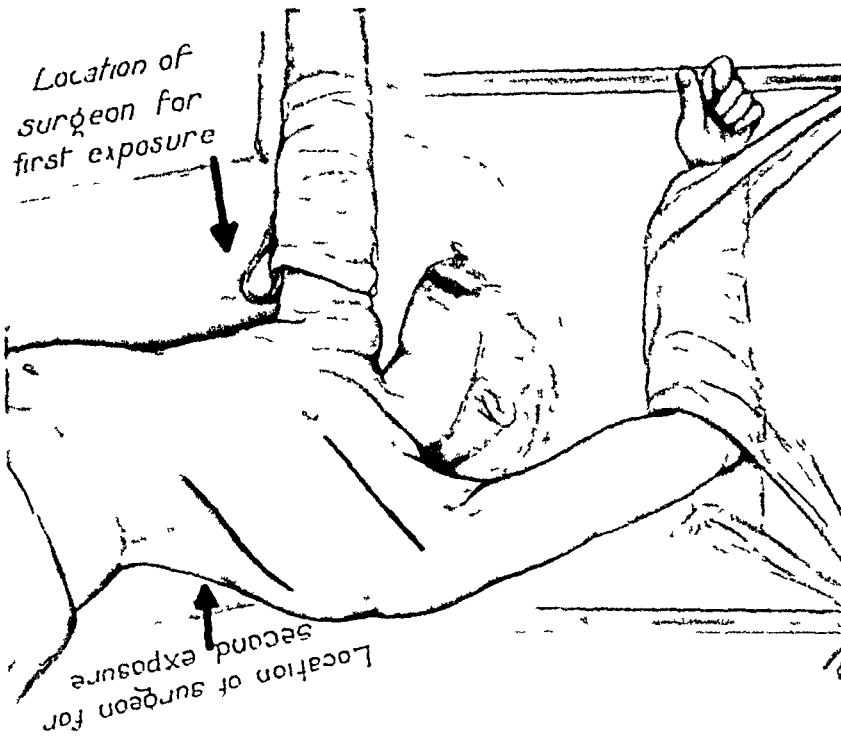


FIG. 3.—The position of the patient during the thoracic operation and the location of the two incisions used. The stellate and upper 8 sympathetic ganglia are dissected free through the upper incision and the remainder of the thoracic trunk the splanchnic nerve the celiac ganglion and at times, the first or first and second lumbar ganglia are removed through the lower incision.

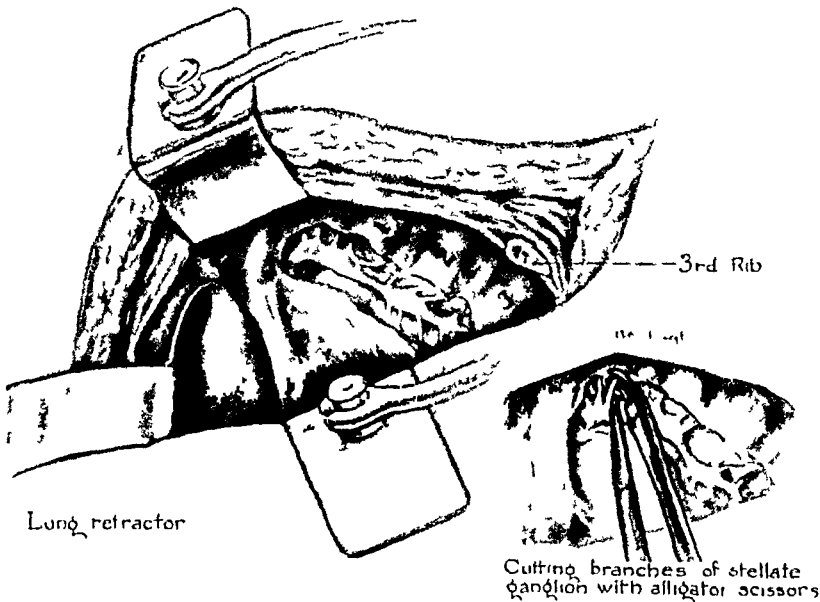


FIG. 4.—The stellate ganglion and the upper thoracic sympathetic trunk exposed through the incision in the bed of the third rib. The overlying pleura has been divided.

free down to the diaphragm. The pleura over the arch of the crux of the diaphragm is divided and the curved tip of the special round diaphragmatic retractor is placed in the arch. Strong retraction on this instrument partly inverts the diaphragm and allows the celiac ganglion to be pulled up through the diaphragm by traction on the splanchnic nerve after blunt separation of the adjacent diaphragmatic muscle. This ganglion is removed as completely

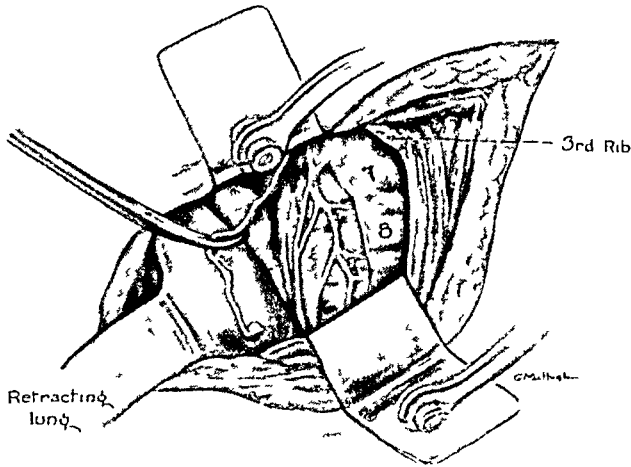


FIG 5—The origin of the splanchnic nerve at the lower end of the operative field exposed by the incision through the third rib bed. The ganglionated sympathetic nerve trunk is freed through this incision down to D7 or D8.

as possible by dividing its distal connections. The sympathetic chain is then followed down through the crux of the diaphragm as far as possible and divided. Success in obtaining ganglia lower than the twelfth thoracic has been variable. Figure 6 represents this portion of the exposure. The thoracic portions of the sympathetic trunk, the splanchnic nerve and the celiac ganglion, and occasionally, also, the first or the first and second lumbar ganglia are thus removed. A medium-sized Pezzar catheter is then inserted into the pleural cavity through a stab wound between the seventh and eighth ribs in the mid-axillary line and the incision is closed. Air is evacuated from the thoracic cavity through the catheter and a negative pressure maintained for four or five days. Figure 7 illustrates a photograph of the specimens removed from the chest of one patient.

Of the 11 patients, eight had the thoracic procedures. One of these died after the first stage and one after the second. Three patients had both the thoracic and abdominal procedures. Brief case reports are presented.

ABBREVIATED CASE REPORTS

BILATERAL THORACIC OPERATIONS

Case 1—J. W., female, single, age 18 at the time of operation. She had been observed to have a blood pressure of 176/124 three and one-half years earlier when seen in the Urology Clinic because of nocturia. Double ureter and kidney pelvis on the

SYMPATHECTOMY FOR HYPERTENSION

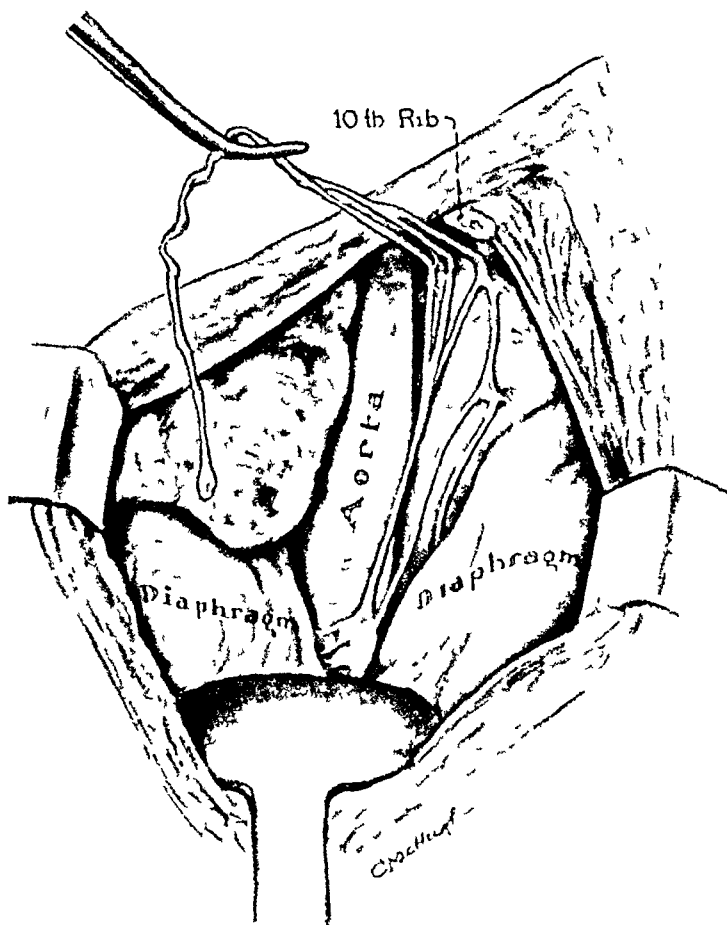


FIG 6—The exposure of the lower end of the thoracic sympathetic trunk and of the splanchnic nerves. The celiac ganglion has been pulled up through the diaphragm. It is removed, as are also as many of the lumbar ganglia as can be reached.



FIG 7—A photograph of the operative specimens removed from Case 10 during the bilateral thoracic operations. The stellate ganglia, splanchnic nerves, celiac ganglia, and, on one side, the first lumbar ganglion are shown.

right was observed. The patient had occasional periods of mild urinary infection and of albuminuria. The blood pressure rose gradually in spite of medical management and restricted activity until it ranged around 200/138. The patient complained of occasional severe headaches. Eyeground examination revealed generalized attenuation of the retinal arteries. There was a bilateral moderate exophthalmos. Rest and 0.6 Gm of sodium amytal reduced the blood pressure from around 212/146 to around 170/120. The two stages of the bilateral thoracic paravertebral sympathectomy were carried out, with an interval of two weeks. The blood pressure between the two operations was as high or higher than before. After the second operation it fell, and three weeks later, at the time of discharge, ranged around 146/98 when the patient was supine. She has been observed seven months and two weeks following the procedure, and her last blood pressures are around 140/90 when supine and 104/70 when standing. Dizziness on standing was noticed during the first month after operation. The patient is now active with no complaints.

Case 2—R. B., female, married, age 25 at the time of operation. She gave a history of nephritis, with blood and albumen in the urine between the ages of four and five. Three and one-half years before operation she developed headaches. Three years before operation she became pregnant and a blood pressure ranging around 180/110 was observed together with albumen and blood in the urine. A therapeutic abortion and sterilization were performed. Six months later the headaches became more severe and a blood pressure of 220/120 was recorded. Under medical management during the next two and one-half years, her blood pressure was observed to range around 180/110. In the hospital during the week before operation, it averaged 168/104. During this period of three years, there was no significant finding in the urine. With rest and 0.6 Gm of sodium amytal her blood pressure dropped from 180/108 to around 140/90. The cold pressor test showed an elevation of 35 Mm Hg systolic and 30 Mm diastolic. Eyeground examination revealed increased tortuosity of the retinal arteries. After the first stage, there was no change in blood pressure but after the second, there was a lowering to around 106/64 during a six weeks' postoperative period of observation. She has now been observed 14 months, during which her blood pressure has ranged around 120/70 supine and 100/64 standing. The patient is active with no complaints.

Case 3—C. D., female, married, age 33 at the time of operation. Eleven and one-half years earlier, during a premature delivery, her systolic blood pressure was recorded at 220 Mm Hg. After delivery, her systolic blood pressure varied from 180 to 220. One year and seven months before operation, she went through an episode of precordial pain, dyspnea, and swollen ankles. Six months before operation, she had a cerebral accident involving the right arm and leg and leaving extensive residual paralysis. Her blood pressure on admission was 242/148. During two weeks in the hospital, before operation it ranged between 286/170 and 200/120. The elevation with the cold pressor test was 20 Mm Hg systolic and diastolic. With rest and 0.6 Gm of sodium amytal the pressure fell from 260/160 to 220/145. Papilledema, hemorrhage, exudation, and other advanced eyeground changes were present. Following the first thoracic operation, there was no reduction in blood pressure. Immediately following the second thoracic operation, the blood pressure ranged around 140/80. The patient, however, did not regain consciousness and 30 hours later developed respiratory failure. Artificial respiration was continued for several hours after which time circulatory failure developed, with death. Autopsy revealed a cavity in the left side of the brain $2.5 \times 1.5 \times 0.5$ cm in length running from the central white matter of the frontal lobe posteriorly to the caudal extremity of the lenticular nucleus. There was generalized cerebral arteriosclerosis with old and recent foci of encephalomalacia and old and recent perivascular hemorrhages in the pons. It is of interest that during the 30-hour postoperative period of reduced blood pressure, the patient excreted 1,600 cc of urine.

Case 4—I. M., married, female, age 38 at the time of operation, and had only one preoperative complaint, that of blurring vision requiring frequent changes in her glasses.

Six months before operation her blood pressure was 220/120. Between then and the date of operation, it ranged around 210/118. In the hospital, the week before operation it averaged 180/114. Eyeground examination revealed only generalized attenuation of the retinal arteries. Rest and sodium amytal lowered the blood pressure from around 180/110 to around 135/90. The cold pressor test elevated the systolic pressure 35 Mm Hg and the diastolic 25 Mm. The two-stage thoracic procedure was carried out. During the 17-day interval between operations, no lowering of blood pressure was observed. It ranged around 150/102 during the four weeks in the hospital after operation. This patient developed a mixed psychoneurosis with secondary depressions. She fixed on the operation as the cause of all of her troubles. Hospitalization was carried out one and one-half, two, and four and one-half months postoperatively because of this psychiatric difficulty. Her blood pressure during these hospitalizations averaged 166/96, 144/96, and 150/100 respectively. She has since been more antagonistic, and one reading, seven and one-half months after operation, was 198/128 lying and 184/104 standing. The last blood pressure readings, 12 months after operation, were 144/102 lying and 112/84 standing.

Case 5—E. R., a poorly nourished male, age 40 at the time of operation. He had consulted a physician four and one-half years earlier because of lack of appetite, dizzy spells, and headaches. His blood pressure then varied between 170/130 and 145/90. It gradually rose, and during the three and one-half years before operation ranged from 206/130 to 176/116. Fatigue, headaches, and dizziness persisted. One year before operation he had a mild cerebral accident following which he could no longer perform his duties as a lathe operator. During the week before operation his blood pressure averaged 178/116. Rest and 0.6 Gm of sodium amytal lowered his blood pressure from 194/120 to around 165/105. The cold pressor test elevated it 24 Mm Hg systolic and 10 Mm diastolic. Examination of the eye revealed irregularity and marked narrowing of the retinal vessels and some arteriovenous nicking. The two stages of the thoracic operation were performed 13 days apart, with no blood pressure lowering between. Sixteen days later the patient was discharged. The postoperative hospital blood pressure readings averaged 126/86. During eight months of postoperative observation the blood pressure ranged around 140/100 supine and 96/74 standing. He has occasionally had mild headaches but the fatigue and poor appetite persist and he considers himself unable to work.

Case 6—H. S., male, age 42 at the time of operation. A year and one-half earlier headaches developed and eight months ago his blood pressure was 190 systolic. Six months before operation a cerebral accident occurred involving the right arm, leg and face and making speech difficult. The blood pressure was 255/145. A month later recovery of the use of the leg began and he was able to walk. There was limited use of his arm at the time he entered the hospital. His blood pressure in the hospital before operation averaged 196/128. Sodium amytal lowered it from around 230/134 to around 160/120. The cold pressor test elevation was 70 Mm Hg systolic and 60 Mm diastolic. Eyeground changes consisted chiefly of constriction of the retinal arteries with tortuosity of the smaller vessels. The patient received the thoracic operations with an interval of 14 days, during which there was no change of blood pressure. He then remained in the hospital six weeks during which time his blood pressure ranged around 146/90. He has been followed postoperatively for eight and one-half months and during that time has had a blood pressure ranging around 150/94 lying and 124/84 standing. He has now no complaints and is active although unemployed.

Case 7—R. E., male, age 48 when operated upon. Four years before his blood pressure was reported to have been around 210/135. His complaints were chiefly fatigue, dyspnea after climbing one flight of stairs, and disturbance of vision. Eleven months before operation, hemorrhage and exudation were noted in the eyegrounds. Six weeks before operation his blood pressure was as high as 272/172. Papilledema, with marked progression of the hemorrhages and exudates, were noted. In the hospital before operation, the blood pressure ranged around 235/158. Rest and 0.6 Gm of

sodium amytal lowered it from around 210/140 to around 185/120. The cold pressor test gave an elevation of 50 Mm Hg systolic and 45 Mm diastolic. Right thoracic sympathectomy was performed. There was, as in the other patients, no lowering of blood pressure following this procedure. Sixteen days later a roentgenogram of the chest revealed the lungs to be clear, and the patient was sitting up out of bed. The second-stage operation was under consideration when he developed pneumonia followed by uremia, and, 21 days later, by death.

Case 8—L. F. M., male, age 50 at the time of operation. Four years earlier he developed severe headaches and noticed occasional dizzy spells. During the last two years, these symptoms became more severe and the systolic blood pressure was over 200. Four months before operation, a cerebral accident occurred with a paralysis of the left arm and leg from which there has since been extensive recovery. The blood pressure was 252/140. During the week in the hospital before operation, it averaged 218/130. Rest and 0.6 Gm of sodium amytal reduced the blood pressure from 228/120 to around 188/100, with two single readings of 166/88 and 150/90. The cold pressor test produced an elevation of 50 Mm Hg systolic and 30 Mm diastolic. Eyeground examination revealed a thickened, slightly blurred nasal nerve fiber layer on the right disk and nicking, hemorrhage and exudation in the retina. Urea clearance determinations were at the lower limits of normal. Following the right thoracic sympathectomy, cardiac decompensation and pulmonary edema developed. These complications cleared up in about two weeks. No blood pressure lowering was observed in the 25-day interval that preceded the second stage. Cardiac and pulmonary complications were also observed after the second stage. During the next five weeks in the hospital, his blood pressure ranged around 156/90 supine. Seven months after operation, he was admitted to the hospital for two weeks during which time his blood pressure readings averaged 160/90. His readings in the out-patient department have been higher, ranging around 172/100 supine and 134/104 standing 12 months postoperatively. This patient while having less energy than formerly has no special complaints and is active.

BILATERAL THORACIC AND ABDOMINAL OPERATIONS

Case 9—A. W., female, married, age 33 at the time of operation. Five and one-half years earlier she developed albuminuria and a systolic blood pressure of 290 in the fourth month of pregnancy. A therapeutic abortion was performed. During the next two years, the patient had several attacks of precordial pain. The blood pressure elevation continued. Dyspnea, palpitation, and ankle swelling had gradually progressed. She was first seen here at that time, and the blood pressure was 240/144. Eyeground examination showed the disks to be pale with hazy margins and tortuous capillaries on their surfaces. Arteriovenous compression, small hemorrhages, and exudates were observed in the retinae. Rest and 0.6 Gm of sodium amytal lowered her blood pressure from 230/128 to 204/118. Cold pressor tests produced an elevation of 20 Mm Hg systolic and 30 Mm diastolic. Thiocyanate therapy was employed for four months with the blood pressure unchanged, averaging around 230/130. A bilateral supradiaphragmatic splanchnic area denervation, as advocated by Peet,⁴ was then carried out by Dr. William Adams. The blood pressure averaged 190/122 for one week and then returned to its previous level. Three months later, thiocyanate therapy was again employed without appreciable effect. Fifteen months later, an attempt was made to complete the sympathectomy using the technic described above. All three stages were employed at one-month intervals. Following each stage, there was some lowering of pressure until after the abdominal operation it averaged for two weeks 174/108. It then gradually rose until at two months it reached an average supine of 220/130. She has been observed 11 months. The last blood pressure reading is 254/154 supine and 192/120 standing. The patient is moderately active with only occasional mild headaches. Swelling of the ankles is again evident.

SYMPATHECTOMY FOR HYPERTENSION

Case 10—L. M., widow, age 40 at the time of operation, and had had headaches for about four years. She suffers from a severe anxiety neurosis that has persisted up to the present time, with only slight improvement. The first blood pressure readings a year and eight months before operation were 248/128 and 280/130. She was hospitalized four weeks at that time, and the blood pressure readings averaged 236/128. Thiocyanate therapy was without evident effect. The blood pressure continued for a year and six months around 250/134 with one high reading of 310/144. During four weeks of hospitalization preceding operation, there was some improvement in the mental state and the average blood pressure was 204/110. Eye-ground examination revealed minimal hemorrhage and exudate and marked nicking but no papilledema. Rest and 0.6 Gm of sodium amytal lowered the blood pressure from around 240/120 to around 160/90. The cold pressor elevation was around 35 Mm Hg systolic and 20 Mm diastolic. The blood pressure during the 12-day interval between the thoracic stages was unchanged. Following the second stage it ranged around 180/96 for two months. The abdominal sympathectomy was then performed. The blood pressure during the next three weeks ranged about the same level. Four months later a single reading was 280/154. The patient was readmitted to the hospital for a week and the blood pressure averaged 192/108. Her latest blood pressure readings, 10 months after the third stage range around 224/124 supine and 160/90 standing. She is active, and states that she feels better.

Case 11—McK. T., male, age 44 at the time of operation. The blood pressure is known to have been elevated for seven years, starting around 180/110 and gradually increasing to around 210/130. The complaints were occasional headaches and attacks of numbness usually unilateral, involving the arms and legs. Eye-ground examination revealed early edema of the disks with marked perivascular sheathing of the retinal vessels. Rest and 0.6 Gm of sodium amytal lowered his pressure from around 200/112 to around 158/90. The cold pressor response was 40 Mm Hg systolic and 70 Mm diastolic. Because of the possibility of an adrenal tumor, the abdominal sympathectomy including division of most of the splanchnic nerves was performed first. Exploration of the adrenal glands and kidneys revealed no gross pathology. Following this, the blood pressure ranged around 158/108 for 20 days, at which time the right thoracic sympathectomy was performed. In the 23 days that preceded the left thoracic sympathectomy, the blood pressure was around 150/102. Following this, it ranged around 128/80 for eight weeks. All of these readings were taken with the patient supine. The patient had a marked postural hypotension, with extreme dizziness, and it was six weeks after the last operation before he could walk about and be discharged. It is too early to evaluate the symptomatic change. Six months after operation his blood pressure readings were 140/100 supine and 76/54 standing.

SUMMARY—A three-stage technic for removal of the thoracic and lumbar paravertebral sympathetic chains including the stellate ganglia, splanchnic nerves, and the major portion of the celiac ganglia has been described. This operative procedure has been employed upon 11 hypertensive patients. Three had only slight organic hypertensive changes, four had had cerebral accidents, three were old, severe long-standing hypertension, and one was a rapidly progressing severe hypertension with renal deficiency. Two of these patients, one with marked brain damage, and one with marked renal damage, died. The bilateral thoracic procedure only was employed in six patients and the three-stage procedure including the lumbar sympathectomy was employed in the remaining three. A complete loss of sweating has not been achieved. The iodine, starch, heat-sweating test has shown occasional patchy areas of sweating.

in the apparently denervated areas in each patient. Figure 8 shows the dark areas of sweating in Case 11 after the three-stage procedure, and in Case 6 after the two-stage thoracic procedure.

This extensive sympathectomy has been demonstrated to be compatible with a relatively normal existence. The patients dress more warmly in cold weather and notice excess perspiration during warm weather in those areas still capable of sweating. Dizziness associated with postural hypotension has

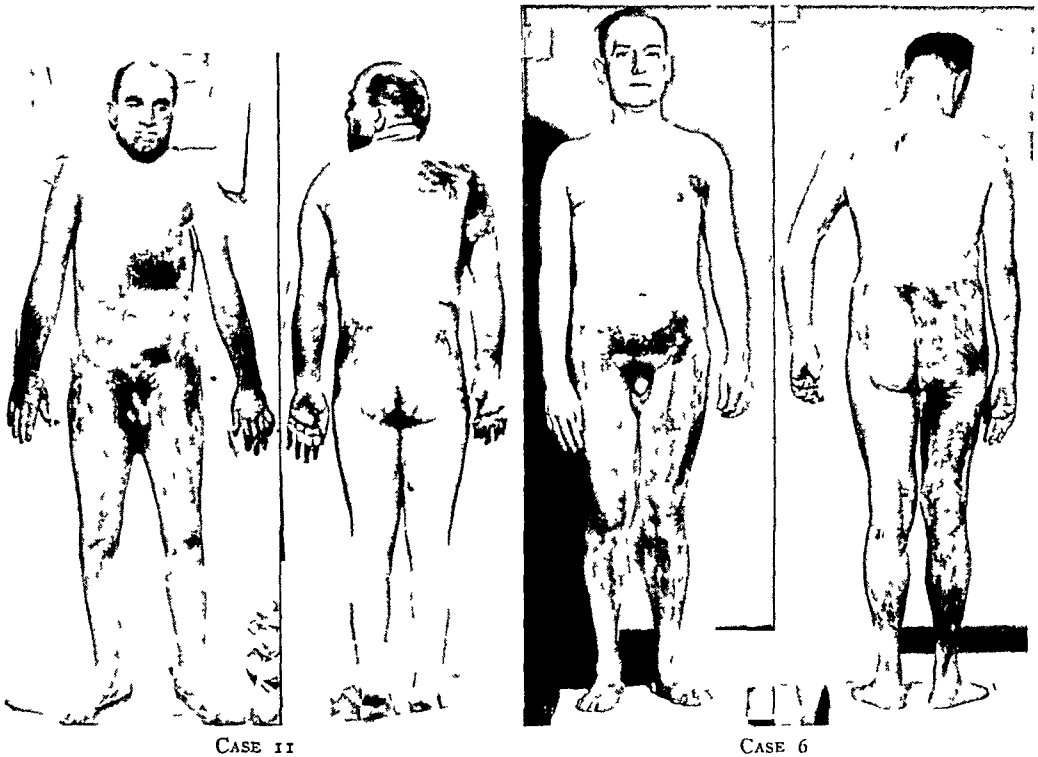


FIG 8—The dark areas of sweating visualized by the iodine starch and heat test in Case 11 after the three stage sympathectomy and in Case 6, after the bilateral thoracic procedure. Areas of sweating are present in the regions supplied by the sympathetic trunks that have apparently been removed.

been troublesome only during the first few months. The bilateral Horner's syndrome has been distressing to only one patient, Case 4. A transient hyperactivity of the bowel has been noticed after each thoracic procedure in many of the patients. The pulse rate has been somewhat decreased. The response to stimuli such as the cold pressor test has been either unchanged or slightly diminished. The blood pressure lowering response to rest and sedation as in the sodium amytal test has been in most instances almost entirely abolished (Chart 1).

Some lowering of blood pressure has been observed on each patient. The lowerings of the blood pressure with the patient supine have varied from a transient one followed by a restoration to about the previous hypertensive level in Case 9, to a lowering to relatively normal values over a period of 14 months of observation in Case 2. The lowering of blood pressure with the

patient standing, sitting, or walking about has been more marked and is present in all patients. The patients have been followed from six to 14 months. No blood pressure lowering was observed after the first thoracic operation in nine patients. This serves as somewhat of a control for nonspecific blood pressure lowering operative effects. The observed blood pressure lowerings seem to be related to the extensive removal of the sympathetic system.

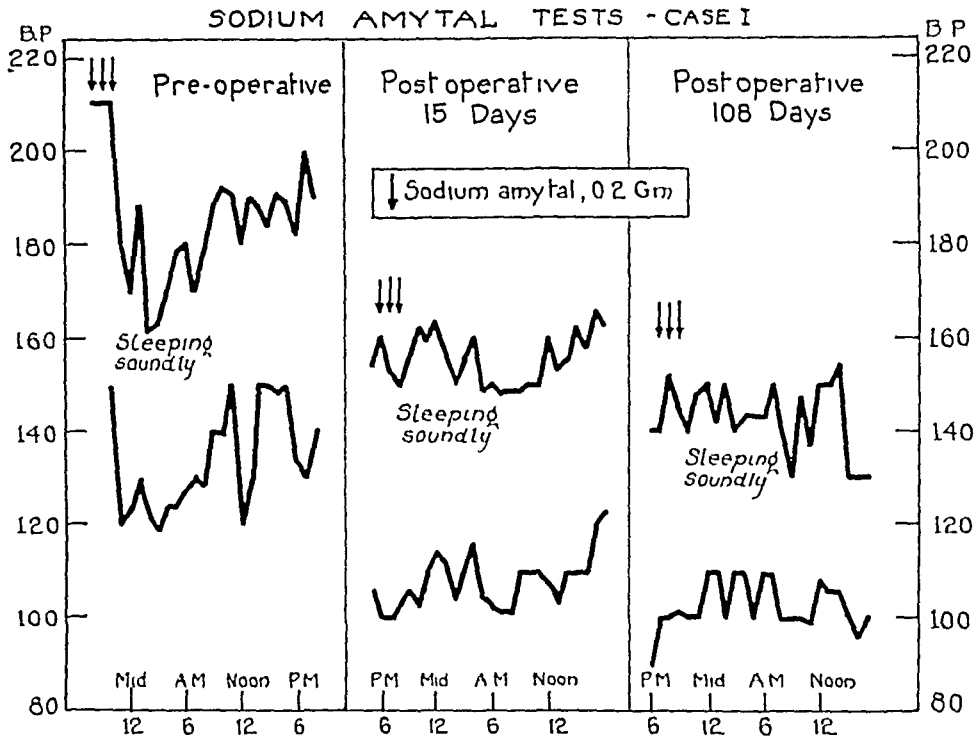


CHART 1—Showing the effect of rest and 0.6 Gm of sodium amytal during the 24 hour test periods on the blood pressure of Case 1, before the bilateral thoracic operation and 15 and 108 days after this procedure. The general blood pressure level is lower. The sodium amytal test after operation produced no additional lowering.

Doctors Alving, Wright Adams, and others¹⁵ have conducted extensive cardiorenal studies on many of these patients before and after operation. They have found no regular significant change in the urea clearance, the ability of the kidney to concentrate urine, venous pressure, or arm-to-tongue circulation time. The heart rate and cardiac output under basal conditions was decreased slightly. Studies of renal blood flow, glomerular filtration rate, and functioning tubular mass have shown no significant change. Renal blood flow increased in one patient and was either unchanged or decreased in the others. They conclude that such lowering of blood pressure as occurs after this extensive sympathectomy is due to a decrease in peripheral resistance. It is impossible at the present time to correlate this alteration of peripheral resistance to any alteration of possible etiologic factors in these patients that might parallel either experimental neurogenic or renal types of hypertension. The rôle that either or both of these factors, together with organic vascular pathologic changes increasing the peripheral resistance may play in clinical hypertension awaits further clarification.

CONCLUSIONS

This is a report of studies in progress of the effect of extensive to total paravertebral sympathectomy in hypertension and no conclusions are drawn as to whether or not this operative procedure will prove to be one of lasting merit. It is a more extensive operation and carries a greater risk than does splanchnicectomy but it appears to lower the blood pressure more consistently. The results are sufficiently encouraging to warrant further studies of the cases already operated upon and further operative trial in selected cases.

The author wishes to acknowledge his appreciation for the cooperation and aid given by Drs Alf S Alving, Wright Adams, Jerome Gans, Louis Leiter, Richard Sternheimer, Alf Haerem and others, of the Department of Medicine who have cooperated in the study and management of these patients.

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DISCUSSION—DR R H SMITHWICK (Boston, Mass.) We have approached this problem from a rather different viewpoint than that which has been presented this evening. Our experience has been entirely confined to a study of hypertension in man. We have felt that hypertension in man, in itself, is a highly experimental and a very complicated problem. There appear to be a number of variable factors which combine to result in hypertension in man. I think there is one thing that we will all agree upon, and that is that nobody knows the cause of hypertension in man.

For this reason, we have felt that the best method of procedure was to start with the simplest operation that we thought might result in reduction of blood pressure. Because of the upright position of man, we have felt that the splanchnic bed must be much more highly developed, in order to maintain blood pressure relatively normal in the various positions than is the case with the dog. Therefore, we thought that it would be advisable, following the lead of Adson and Peet, to denervate the splanchnic bed and to see what the results of that procedure were and, if we found evidence from our studies that further surgery was indicated, to proceed on the basis of evidence derived from our studies in man, rather than from evidence deduced from experimental work.

A chart was shown by the speaker which represented what he considered a good result from partial denervation of the splanchnic bed. Our criterion for partial denervation of the splanchnic bed is that there is no significant change in blood pressure as the patient changes position. Our criterion for complete denervation of the splanchnic bed is a striking and precipitous fall in blood pressure as man shifts from the horizontal to the vertical position.

This patient is characteristic of the good results that we obtained, in a series of approximately 70 cases followed up to four years, by partial denervation of the splanchnic bed by one method or another. This happens to be the result of a supradiaphragmatic splanchnicectomy by the Peet technic. The patient is in the early stage of the disease, is very young, and fulfills all the qualifications that we know of that would indicate a good result. Her blood pressure has been within normal limits, except for possibly slight diastolic hypertension, for approximately four years. One might wonder what further effect there would be if this patient were totally sympathectomized. Our feeling has been, and we have been interested in the question of more extensive sympathectomy for a number of years, that faced with a result like this, in our present stage of ignorance concerning this disease, we were not justified in proceeding with further denervation.

In these 70 cases of partial denervation of the splanchnic bed, our medical department came to the conclusion that nine and one-tenth per cent had results comparable to this, that is, unquestioned persistent and significant lowering of blood pressure. That figure is considerably lower than has been reported by others, with much greater experience.

Some patients do not respond to partial denervation of the splanchnic bed, and in these, we wondered whether further denervation, more extensive sympathectomy, might be helpful. A chart was here shown of a patient who was one of a number of failures of partial sympathectomy, and decided to proceed further. First of all, before any surgery, she was followed in the out-patient department for several months, and while under observation developed an hemiplegia. She recovered from that satisfactorily, was followed several months more, and we decided to operate. She had a supradiaphragmatic splanchnicectomy in two stages, again the Peet technic. We felt there was no significant blood pressure response following the operation.

We decided to proceed further. I might say that in other cases before this, instead

of proceeding downward, as we did in this case, we proceeded upward, in order to increase the magnitude of the operation to include the lower half of both thoracic sympathetic chains, not including the heart. In no case who had failed to respond to the Peet operation did we get any significant response by proceeding higher in the thorax. On the other hand, by proceeding downward, we did, in a number of cases, observe a significant response. In other words, by adding bilateral lumbar sympathectomy in two stages we derived a significant response. Thus, in addition to the Peet operation, the first, second, and third lumbar ganglia were removed on both sides.

So we came, after a period of trial and error, to feel that complete splanchnicectomy, which resulted in postural hypotension in every case, might offer more for some of these individuals, and this was accomplished by removing the sympathetic trunks from D_6 to L_1 or L_2 , inclusive, both sides, together with excision of the great splanchnic nerves from the semilunar ganglia to about the midthoracic level.

A chart was here shown demonstrating a typical good result from this procedure, showing a reduction of blood pressure to normal for two years in a patient with malignant hypertension.

We also wondered whether in patients who did not respond to the combined supra- and intradiaphragmatic operation further sympathectomy would be beneficial. A chart was here shown of a patient who had been sympathectomized totally. This was undertaken in seven stages, and we felt there was no significant response.

Our impression is that in patients who do not respond to complete splanchnicectomy, further denervation probably will not result in significant lowering of blood pressure. On the other hand, we feel that in those who do respond to complete splanchnicectomy, we are not justified in proceeding with further sympathectomy in the present state of our knowledge. Such indications may arise in time, but it is our notion that they had best be deduced from the study of hypertensive patients rather than from experimental animals.

Our percentage of significant and persistent lowering of blood pressure following complete splanchnicectomy, as contrasted with partial splanchnicectomy, is as 65 per cent is to 91 per cent, at the present time.

In commenting upon the paper this evening, I think we have been presented with a very detailed and valuable study in a small series of patients. It is difficult to compare this statistically at this time with other larger series. However, I think that Doctors Grimson and Phemister are to be congratulated on the care and the detail with which they have studied their cases. I think that time alone will tell whether total sympathectomy has anything more to offer these patients than less than total sympathectomy.

DR GEORGE M. CURTIS (Columbus, Ohio) From carefully controlled clinical studies such as these, and particularly from those which have grown out of previous laboratory experimentation, much clinical physiology may be learned in evaluating the effects of the application of newer operative procedures. Thus the application of pneumonectomy to the treatment of lung carcinoma has led to the operating table demonstration of the low blood pressure normally present in the pulmonary artery.

In sympathectomy combined with ganglionectomy in the treatment of hypertension, we are thinking mainly of vasomotor effect, although secretory effects, and particularly those from the adrenal, have received due consideration. Nevertheless, other visceral mechanisms are also involved when the lower thoracic sympathetic chain and splanchnic nerves are removed. Thus, there is an ensuing increased motor activity of the stomach, perhaps due to the then unopposed action of the vagi (Arch Surg, 32, 577, 1936).

However, we should be careful not to lose sight of the sensory fibers from the upper abdominal viscera. Some of these pass upward through the splanchnic nerves, along the ganglionated cord and through the white rami to the dorsal ganglia and spinal cord. In this surgical field, opportunity is thus afforded to learn something of the sensory impulses they carry. It may be that they act in an important manner in the sensory defense of the upper abdomen.

Thus a number of clinical symptoms are closely associated with hypermotility of the human stomach. Among these may be mentioned nausea, upper abdominal distress, or cramps, and certain types of "gas pains." Moreover, hypermotility may be induced by morphine with the production of upper abdominal distress and then controlled together with the discomfort, by atropine.

Yet in the hypermotility subsequent to bilateral splanchnic resection, our few patients have not noted these accompanying disturbing sensations, such as would ordinarily accompany such evidence of increased gastric activity. Is it possible that excision of the splanchnic nerves has also removed an important sensory mechanism in the interpretation of visceral change in the upper abdomen? The answer to this question obviously has a practical clinical bearing and merits further clinical attention. Perhaps the speaker may also have a solution to the problem.

Our own consideration of the matter may be presented by showing a few charts.

Chart 1 shows the method which we have used for studying the motor activity of the human stomach following unilateral and bilateral splanchnic resection. The ink writer here obviates the smoked drum and makes this work possible in the clinic along with the white linen.

This is a roentgenogram showing the position of the balloon in the stomach, connecting through this tube to the kymograph.

Chart 2 is that of a patient with an obstructive duodenal ulcer, showing a marked increase in gastric motility, and with it was associated severe abdominal pain. Later, ensued a spontaneous remission of the increased motility with cessation of the upper abdominal distress.

Chart 3 is that of a patient who had, postoperatively, what are commonly called "gas pains" or cramps and as these occurred he pressed a button, recording these simultaneously with increases in peristaltic action of the stomach. Atropine intravenously, 1/150 gr, at this point was given, with cessation of the distress and the associated increased contractions.

Chart 4 is that of patient with duodenal ulcer, to whom morphine, 1/8 grain intravenously, was given at this point. Note the ensuing increased activity, both in frequency and amplitude. This was accompanied by definite upper abdominal distress. After giving atropine, 1/150 gr, intravenously, there ensued cessation of the increased motility and disturbed sensation. Then prostigmine 1 to 2,000 was given at this point, which reversed the atropine effect and induced motility again. This increased in amplitude and frequency and its occurrence was accompanied by pain. Ephedrine at this point decreased the motility with an accompanying disappearance of the uncomfortable sensation. Thus, we would think that associated with gastric hypermotility there is usually abdominal pain or distress or discomfort (Trans West Surg Assn, pp 447-475, 1938).

Chart 5 is that of a patient who had previously had a resection of the left splanchnic nerves and later of the right splanchnic nerves. This operation, after the technic of Peet, was undertaken in two stages. Subsequent to this, there occurred a marked and persistent hypermotility of the stomach. You see here the increase in amplitude and frequency, which lasted for five hours. We have seen this increased activity persist for a period of six hours, with no complaint of discomfort or of other sensations ordinarily associated with hypermotility, whether occurring spontaneously or induced by morphine. This is another curve made from this same patient. Note the increase in amplitude of the peristaltic waves. Yet this patient did not complain of upper abdominal distress at that time (Am Jour Physiol, 120, 356, 1937).

Chart 6 is that of a patient in whom a bilateral splanchnic resection was performed, according to the Peet technic. You see ensuing increased gastric motility. Yet with this hypermotility there was likewise no upper abdominal distress.

Thus, it would appear that the splanchnic nerves carry certain visceral sensations to the central nervous system, and that these are interrupted and, consequently, not interpreted following bilateral splanchnic resection. The clinical import is obvious, and further consideration seems warranted.

DR MAX M. PEET (Ann Arbor, Mich.) I believe that we ought to study our hypertension patients, both before and after operation, from every standpoint, not just blood pressure. We ought to know the changes in the retina, the changes in the kidney, and in the heart. So we have studied all our patients from every possible standpoint. We have felt, as the others have, that the work is still experimental in many ways, and we could best determine its actual value by using one particular surgical procedure. We have operated upon some 700 patients now, using a bilateral supradiaphragmatic splanchnicectomy with the resection of a long segment of the greater splanchnic nerve and excision of the tenth, eleventh, and twelfth thoracic sympathetic ganglia. Often when pulling up on the greater splanchnic, we actually see the top of the celiac ganglion.

The excised portion of the greater splanchnic nerve extends from the eighth or ninth vertebrae to the diaphragm and measures, after removal, 10 to 15 cm in length. Excision of such a long segment probably prevents regeneration. Occasionally, the ninth thoracic ganglion is readily exposed and when this occurs it is removed with the tenth and eleventh. Sometimes, the twelfth is deeply imbedded in the diaphragm, making its excision impossible. Under such circumstances, we have always cut the twelfth ramus, even though the exposure of this ramus required rather extensive division of the vertebral attachments of the diaphragm.

To rule out possible differences in individual technic, all the patients included in our very thorough follow-up studies were operated upon by me. All have been studied preoperatively and again at a minimal postoperative period of at least nine months by the medical, cardiac, ophthalmologic, and roentgenologic departments of the University Hospital. Pre- and postoperative studies included blood nonprotein nitrogen, water concentration, and urea clearance determination, electrocardiograms, orthodiagrams, and teleoroentgenograms, fundusoscopic examinations, and numerous blood pressure readings from both arms.

Only by such a thorough study can we evaluate any therapeutic procedure. Many of our patients have been studied repeatedly for several years. The longest postoperative period studied in any one patient, a man who before operation had a severe malignant hypertension, is seven years.

I submit the following tables from a paper on the Surgical Treatment of Hypertension, by Peet, Woods, and Braden (JAMA, 115, 1875-85, November 30, 1940), to show you some of the results of bilateral supradiaphragmatic splanchnicectomy. I believe these are as good as those obtained by the much more formidable procedure of total or sub-total sympathectomy. The latter cannot as yet be definitely evaluated since the series is small, complete studies have not been made, and too short a postoperative period has elapsed.

TABLE I
BLOOD PRESSURE

	Number	Per Cent
Cases studied nine mos. or later postoperatively (including deaths)	290	100
Reduced (more than 40 Mm. systolic and 15 Mm. diastolic)	149	51.4
Unchanged	134	46.2
Increased (more than 10 Mm. systolic and 5 Mm. diastolic)	7	2.4
Cases with no data or dead before nine mos. postoperatively	60	

If the 60 patients concerning whom no data were obtained or who died before nine mos. are considered as unchanged or worse, the percentage of patients with significantly reduced blood pressure in the whole group of 350 cases becomes 42.6.

Table I shows the results of splanchnicectomy in a series of 290 patients followed from nine months to seven years. We have not considered any patient under nine months. You notice that of 290 consecutive patients 149, or 51.4 per cent, have had a reduction in blood pressure of more than 40 Mm. systolic and 15 Mm. diastolic, 46 per cent were unchanged. It is possible that some of the latter might be improved further by either a higher thoracic or a lumbar ganglionectomy. Only 2 per cent have increased here.

TABLE II
ANALYSIS OF PATIENTS WITH SIGNIFICANTLY REDUCED BLOOD PRESSURE

	Number	Per Cent
Number of cases studied	149	100
Reduced to normal	56	37.5
(130/90 for ages 20 to 40)		
(150/100 for ages 40 to 70)		
Markedly reduced (but not to normal)	15	10.1
(More than 80 Mm. systolic and 25 Mm. diastolic)		
Reduced (but not markedly or to normal)	78	52.4
(More than 40 Mm. systolic and 15 Mm. diastolic)		

Thus of those cases in which there was significantly reduced blood pressure 47.6 per cent were reduced to normal, markedly reduced or both.

Of the 149 cases that showed worth while reduction, 37 per cent have had reductions to what our medical department considered normal. In other words, these patients

SYMPATHECTOMY FOR HYPERTENSION

have had a normal blood pressure at a postoperative period from nine months to seven years. Certainly this group of patients, representing 37 per cent of those with a significant reduction in blood pressure, did not need a more extensive sympathectomy.

The blood pressure was considered as markedly reduced but not necessarily to normal if the reduction was more than 80 Mm systolic and 25 Mm diastolic. These constitute 10 per cent. Those reduced more than 40 Mm systolic and 15 Mm diastolic but not markedly or to normal, constitute the remaining 52 per cent. It is significant that nearly half of those with a reduction in blood pressure had such a striking result as to be classed as either markedly reduced or reduced to normal.

I might remark that all the preoperative readings were made while the patient was quiet, usually in bed, while the postoperative readings were made while the patient was active and going through various tests. There is no postural change in blood pressure after supradiaphragmatic splanchnicectomy and resection of the lower thoracic sympathetic chain.

As stated before, we not only study the blood pressure but also the eye changes, cardiac condition, renal function, symptomatology, and ability to work.

TABLE III

SUMMARY OF RESULTS OF SPANCHNICETOMY PERCENTAGE OF CASES STUDIED SHOWING IMPROVEMENT (FROM NINE MONTHS TO SEVEN YEARS AFTER OPERATION)*

	Per Cent
Blood pressure	
Reduced to normal	11.7
Markedly reduced (but not to normal)	7.6
Total cases significantly reduced	51.4
General disability	
Symptoms improved	86.6
Complete recovery incapacitation	55.5
Total cases with improvement incapacitation	81.3
Eyegrounds	
Disappearance of papilledema when present	73.8
Total cases with improvement	69.4
Heart	
Heart size diminished	64
Electrocardiogram improved	53.4
Renal function	
Urea clearance improved	52.2
Urine concentration improved	44.8

* Statistics include those patients who showed improvement but who subsequently died.

Table III shows a summary of 350 consecutive hypertensive patients treated by bilateral supradiaphragmatic splanchnicectomy and lower dorsal sympathetic ganglionectomy. Fifty-one per cent had a worthwhile reduction in blood pressure. Symptoms were improved in 86 per cent. Papilledema was absent in 73 per cent of those who had choked disks before operation. Heart size was diminished in 64 per cent. The kidney function was improved as follows: Water concentration, 44.8 per cent; urea clearance, 52.2 per cent. Complete recovery from incapacitation occurred in over 55 per cent.

If we are going to evaluate any procedure for the treatment of hypertension, we must show not only improvement in blood pressure but improvement in heart size, in kidney function, and in other ways. Bilateral supradiaphragmatic splanchnicectomy certainly fulfills these requirements as shown by the above statistics.

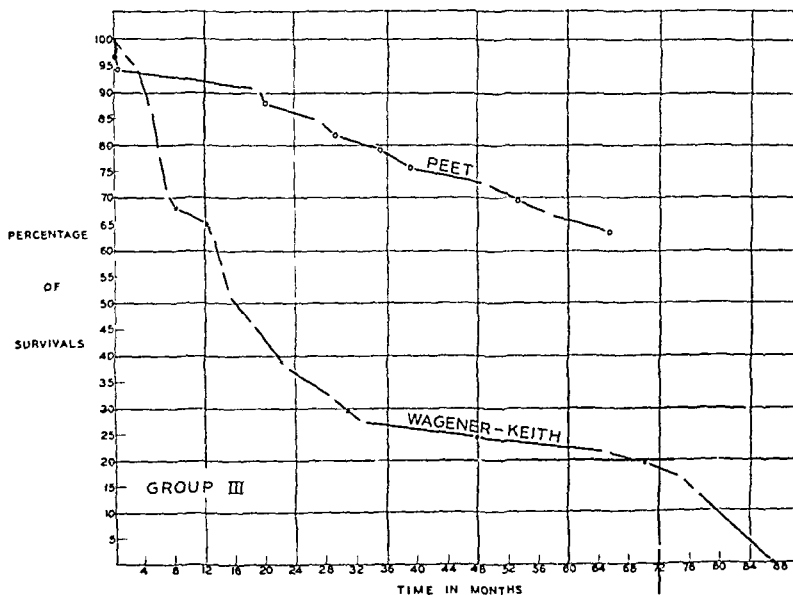
Recently we have compared our mortality after a five- to seven-year postoperative period with the Keith-Wagener table of similar patients treated medically. These cases have been grouped according to the preoperative ocular findings. Graphs 1 and 2 are from a paper by Woods and Peet which will appear in the Journal of the American Medical Association.

Group III represents a very serious type of hypertension manifested by spasm of the retinal arteries, hemorrhages, and often exudates. It will be noted in Graph 1 that the mortality in Group III when treated medically is very high. The same group when treated by splanchnicectomy has a much lower mortality.

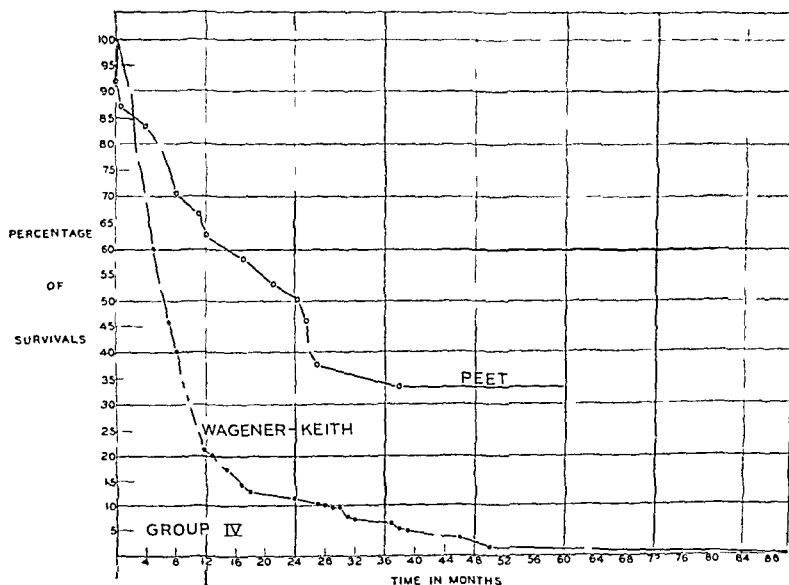
Group IV (Graph 2) represents the so-called malignant type of hypertension and is manifest by papilledema in addition to the retinal changes found in Group III.

(Graph 1) The patients in this group have an exceedingly poor prognosis. It will be noted in Graph 2 that the majority of these patients died within the first year under medical treatment. The mortality in the surgical group is much higher than in any of the other groups treated surgically, but is much more favorable than the corresponding medically treated group.

I believe the data here submitted demonstrates the value of bilateral supradiaphragmatic splanchnicectomy, with resection of the lower thoracic sympathetic ganglia.



GRAPH 1



GRAPH 2

DR ALFRED ADSON (Rochester, Minn.) About ten years ago, I was prompted to devise a procedure to alter the blood pressure of patients suffering from essential hypertension. The operation was based on the principle that blood pressures decrease when high spinal anesthesia is employed. The intent was to reproduce changes similar to

those that occur at the time spinal anesthesia is produced. It consisted of bilateral ventral rhizotomy which included the roots on both sides from the sixth thoracic to the second lumbar vertebrae inclusive. It was performed for the specific purpose of interruption of the vasomotor nerves in the hope that such a procedure would relieve peripheral resistance due to vasospasm. Fortunately, some satisfactory results were obtained. The magnitude of extensive laminectomy and rhizotomy stimulated me to alter the procedure in order to make it less shocking. The next procedure that I devised is bilateral subdiaphragmatic, extraperitoneal resection of the splanchnic nerves with the portion of the celiac ganglion and removal of the lumbar sympathetic trunks, including the first and second lumbar ganglia.

The results of this operation appeared to be equally as good as those that followed extensive rhizotomy. However, it soon became apparent that not all patients responded equally well to the operation. Those who obtained the best results were those whose blood pressure receded to near normal values on rest in bed and who received sodium amytal prior to operation. It also became apparent that the relief of clinical symptoms often was greater than the actual reduction of blood pressure. Patients who had beginning arteriosclerosis and those who already had sustained irreparable damage to the cardiorenal system obtained only temporary or no relief from extensive sympathectomy.

Although various approaches and procedures are employed to interrupt the vasomotor control of a large vascular region, the problem of surgical treatment still remains one of experimentation since Goldblatt, Page, and many others have shown that ischemia of the kidney with the resulting development of a vasopressor substance results in a state of hypertension that is not amenable to sympathectomy. Until such time that an antipressor substance can be produced and administered with safety, I believe we are justified in continuing extensive sympathectomy. It should not be employed indiscriminately in the light of our experiences. May we hope that the operation suggested by the essayist will be more effective than those operations that are being employed.

DR LOYAL DAVIS (Chicago, Ill.) As Doctors Grimson and Smithwick have pointed out, the question of hypertension is a very difficult one and none of us knows all of the exact factors involved in its production. For this reason, it is important that we have a good understanding of what essential hypertension means to each of us before we can understand one another and our results. For us, the term "essential hypertension" includes those cases of chronic hypertension which neither clinically nor anatomically can be demonstrated to have evolved from an antecedent inflammatory disease of the kidneys or from urinary obstruction. In addition to a high systolic and diastolic blood pressure, the changes in the blood chemistry and the clinical stages of the disease are the important factors which must be studied.

In our own experience, the majority of patients with essential hypertension react favorably to the correct administration of potassium sulphocyanate, but there is a group of patients who are resistant to the cyanates and it is to this group that we have devoted our attention in an attempt to do something for them surgically. We have reported upon the fact that many of the patients who are resistant to the cyanates become sensitive following a bilateral supradiaphragmatic splanchnicectomy. In our second series, we are now performing a supra- and infradiaphragmatic section of the splanchnic nerves and removal of the first two lumbar sympathetic ganglia. As yet, it is too early to report upon the results in these patients but we have the impression that this combined operation is more effective.

We are interested in knowing whether or not Doctor Grimson's experimental animals showed an increase in the hematocrit reading, blood protein, and cholesterol levels in addition to their high blood pressures. This is true of the hypertension produced experimentally by ischemia of the kidneys, and, in our opinion, must be present to be correlated accurately with hypertension in man. In our own laboratory, we were able to produce hypertension in the same manner as has Doctor Grimson, but the blood chemistry studies on those animals were never analogous to the blood chemistry findings in clinical hypertension.

It is only by adding together all of the results from the various surgical procedures which are being carried out on man and the experimental investigations, that we will be able to come to some understanding about a problem which is a very difficult one.

DR NORMAN E FREEMAN (Philadelphia) I have been following the work of Doctors Grimson and Phemister with great interest. In our own studies, we were first interested in attempting to prevent the renal type of hypertension by sympathectomy. Four years ago, Doctor Page and I found, just as Doctors Grimson and Phemister have found, that total sympathectomy, including cardiac denervation, did not prevent the rise in blood pressure produced by constriction of the renal artery in the dog.

Three years ago, with Doctor Jeffers, I undertook some experiments on how little of the sympathetic nervous system it was necessary to remove in order to prevent the reflex nervous hypertension which took place from raising the intracranial pressure. We found, as Doctors Grimson and Phemister found, that upper thoracic or lower thoracic sympathectomy alone did not prevent it, but when we combined the two or performed total sympathectomy, the rise in blood pressure from raising the intracranial pressure could be prevented.

On analyzing our results further, we finally found it was necessary to remove only the sympathetic nerves from the heart and to exclude reflex nervous adrenal secretion in order to prevent this type of hypertension. In other words, we could leave in both sympathetic chains from the sixth thoracic to the fifth lumbar, provided we had excluded the adrenal secretion, either by taking out one adrenal and denervating the other, or taking out one adrenal and injecting novocain into the medulla of the other gland.

It would seem from the analogy of the development of malignant hypertension in patients and malignant hypertension in dogs after constriction of the renal artery, that there is a close relationship between the experimental hypertension of Goldblatt and clinical hypertension. On the other hand, I do not think that the nervous influence has been excluded. I think it may be possible that the nervous influence produces its effect by way of renal vasoconstriction. In our own clinical work, we have followed the technic of thoracolumbar sympathectomy, suggested by Smithwick, in order to provide as complete as possible a sympathectomy of the renal area.

DR GEORGE J HEUER (New York, N Y) In view of the references to the effects of various surgical methods of treatment made by other speakers, I should like to refer to the results we thus far have obtained with the operation of anterior root section. In 19 patients with essential hypertension, five or more years have elapsed since we performed this operation and we are, therefore, in the position of stating the five-year results obtained. When we consider the course of the disease, its progressive nature, its eventual outcome, its tendency to recur, if I may so speak of it, after operative treatment, we may liken it to malignant disease, and in appraising methods of treatment we should hesitate to speak of results which have not extended over a five-year period. Of the 19 patients operated upon, five or more years ago, 12 are dead. Of the 12, two lived to within a few months of five years, one lived almost four years, one lived three years, and the remaining eight from a few months to one and one-half years. Of the 12 dying, five died as a direct result of cerebral hemorrhage, seven died of cardiac disease associated with uremia. While these patients lived, four showed marked improvement in their subjective symptoms, others showed moderate improvement. With respect to their blood pressures (last observations before death), two showed the same systolic and diastolic pressure as before the operation, and ten showed a reduction in both systolic and diastolic pressure. The reduction in systolic pressure varied between 20 and 90 Mm Hg, and averaged 50 Mm Hg, the reduction in diastolic pressure varied between 20 and 40 Mm Hg, and averaged 27 Mm Hg. When one studies the causes of death it would seem, in this group, that such reduction in blood pressure did not alter the course of the disease.

Of the seven patients in this series who are now living, all are alive six years, and six are alive from six to seven years after operation. They have all been examined recently. They appear to be in remarkably good condition. They are free from the subjective symptoms they previously had, and are all active and following their usual occupations. With respect to their blood pressures, in two, the blood pressures are normal, in three, elevated (systolic 180, diastolic 105), in two, definitely elevated (systolic 210/220, diastolic 100/120). It would appear that in some of these patients the course of the disease has been interrupted and life prolonged, but it is clear that even a longer period of observation is necessary before final results can be stated with assurance.

DR KLITH S GRIMSON (Chicago, closing) I am not in position to discuss the effect upon hypertension of splanchnicectomies of the various types. There have been more than 1,800 operations of this type performed and, as time goes along, an accurate postoperative study should properly evaluate the procedure. The high incidence of indifferent results reported after splanchnic area denervation, and the marked experimental difference between partial and total sympathectomy have led to the operation of total paravertebral sympathectomy in man. It is hoped that better results may be obtained by this procedure.

I believe that the discussers have brought out the differences of opinion concerning the various types of splanchnicectomy, and, of course, the medical men have still further differences of opinion. Studies of hypertensive patients are very difficult to control, and there has been considerable controversy about the effect of splanchnic area denervation. We have had little experience with this operation.

Doctor Curtis asked about gastric motility and sensation. This operation, as it has been performed, includes the celiac ganglia, in an effort to prevent regeneration. Motility studies have shown no abnormality. It is surprising how well patients can get along without the sympathetic system.

Doctor Davis asked about thiocyanate therapy. That has not been given to these patients postoperatively because as yet we have not felt that they have needed it. There is one exception. That is the patient I first spoke of, who had had a period of thiocyanate with no result, sympathectomies with very indifferent results, and then sulphocyanate—again, with still no result. There certainly is a chance that the peripheral resistance may have become so fixed in this patient that no mechanism which can be attacked is going to relax it.

I have not time to go over all of the discussion, except to say that we do fully recognize that these results are very early. We report them in the interest of an attempt to get at the mechanism of the hypertension, and in the hope that perhaps more might be accomplished by this procedure than by partial sympathectomies.

ASCORBIC ACID AND HUMAN WOUND HEALING*

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DURING the last few years, surgeons have been paying increasing attention to all the circumstances that play a part in the successful healing of operative and other wounds. The mechanical factors involved have been studied in great detail by two groups led, respectively, by Harvey,¹ and Whipple.^{2,3} Harvey, in particular, has shown how much strength can be expected in a given wound, at a given time, with a given type of suture material, properly placed. Eighty per cent of the disruptions that formerly occurred in Whipple's clinic have been avoided by changes in technic. Very widely over the country, there has been a steady shift in technic toward finer suture materials and especially toward fine silk and cotton, and to more suitable placing of sutures. With this change, better results are certainly being achieved.

During the same period of time, two chemical factors, plasma protein and ascorbic acid, that effect healing, have also come into prominent attention. Harvey showed an increased rate of healing on a high protein diet. Whipple,⁴ Carrel,⁵ and Ravdin,⁶ have shown that a slight degree of lowering of the level of plasma protein may delay healing. A marked lowering will delay it enough so that even the most meticulous care in the type and placing of sutures may not result favorably.

More recently, the importance of ascorbic acid has been recognized in wound healing. Lanman and Ingalls,⁷ Archer and Graham,⁸ and Ingalls and Warlen⁹ made the earliest observations on surgical patients in which plasma ascorbic acid determinations were made. Lanman and Ingalls,⁷ and also Taffel and Harvey¹⁰ have studied the tensile strength of experimental wounds in animals with scurvy. Partial scurvy delays healing in animals. More recently, Wolfer and Hoebel,¹¹ Bartlett, Jones, and Ryan,¹² Holman,¹³ Hartzell, Winfield, and Irwin,¹⁴ and Lund and Crandon¹⁵ have made further observations on man. All of these authors have found that many of their patients have subsaturation levels of ascorbic acid in the plasma. Some of them offer the opinion that a low plasma ascorbic acid level indicates a degree

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of deficiency that may cause failure of healing Crandon, Lund, and Dill¹⁶ showed that slight or even moderate deficiency in ascorbic acid reserves did not effect the healing of an experimental wound in a human. They also showed that plasma ascorbic acid determinations were not a good index of deficiency and that the plasma vitamin C level could be zero, and yet the patient might be far from having clinical scurvy, and his wound might heal quite normally. This indicates that the vitamin C reserves in the tissues or in the tissue cells and not the level in the plasma are the determining factor for healing. They also confirmed the finding of Butler and Cushman,¹⁷ and showed that ascorbic acid determinations, made on leukocytes, gave a much more certain evidence of the degree of depletion of the body reserves of this substance. If the leukocyte level is below 4 mg per 100 Gm, we consider the patient to be close to scurvy. (The normal value is 30-40 mg per 100 Gm.)

Another method of studying the reserves of ascorbic acid is by saturation tests. Such tests may be carried out by measuring the plasma levels, the urinary excretion, or both, before and after test doses of the vitamin which may be given either by mouth or intravenously. Studies of the degree of ascorbic acid deficiency, by making saturation tests, have been made by many investigators. Wright, Lilienfeld, and MacLenathan,¹⁸ Wright and MacLenathan,¹⁹ and Portnoy and Wilkinson,²⁰ are among those whose data are very useful. Crandon, Lund, and Dill also performed a saturation test at the completion of their experiment, and determined the changes in the plasma and leukocyte ascorbic acid levels as scurvy was relieved. It is the authors' belief that one of the best and simplest saturation tests is performed by making daily plasma determinations 24 hours after daily doses of 1 Gm of the vitamin given either intravenously or by mouth. Tested in this way, a moderately severe case of scurvy showed a zero level in the plasma the day after the first dose, 0.1 mg per 100 cc, after the second, 0.4 mg, after the third, 0.6 mg, after the fourth, and 0.8 mg, after the fifth dose. The leukocyte ascorbic acid determinations on the first four days showed 3, 15, 30, and 32 mg per 100 Gm, respectively. Other cases studied by us failed to show any rise in the plasma level until after the fourth dose. Other laboratories have made similar findings. Provided intestinal absorption is normal it makes little difference whether the test dose is given by mouth or intravenously. Doses of ascorbic acid in smaller amounts may also be given. In some of our earlier work, various doses of less than 1 Gm were tried. A good idea of the vitamin deficiency may be gained by such doses, but the period of testing is prolonged.

It is always preferable to know what the levels are before treatment is started, but if one is sure of the doses given one can sometimes calculate the degree of deficiency without such information. For instance, if a patient had a plasma level of 0.3 mg per 100 cc the morning after the third daily intravenous dose of 1 Gm of ascorbic acid, one can be quite sure that a severe deficiency was present at the start of the treatment.

Another way of estimating the amount of deficiency is to calculate the amount of the vitamin taken by the patient in his food. This is less accurate, much more troublesome and more time-consuming than other methods, but has the great advantage of being available to any doctor and not necessitating any very delicate, expensive laboratory tests.

Dietary histories were taken on all the cases reported below. To evaluate such data the vitamin content of the foods must be estimated by calculation. These calculations were made from the data in *Vitamin Content of Foods*.²¹ We believe that patients may maintain fair but not saturated reserves with an intake of 25 mg of ascorbic acid per day,¹⁶ but that when an intake below 10 mg has prevailed for a long time that the reserves probably become severely depleted.

Two developments of the same general nature, but different in degree, occur as a result of poor healing after abdominal operations. One of these is postoperative hernia—due to failure of the fascia—and the other is disruption which is due to failure of all layers of the wall to heal. Both of these developments have been studied.

Postoperative Hernia Following Gallbladder Operations—Lund and Crandon showed that various plasma vitamin C levels had no relation to the development of postoperative pulmonary complications. Fifty-eight of the same patients presented in that study, returned to the Follow-Up Clinic from three months to one year after discharge, and were studied for the presence of postoperative hernia by one of us (J. H. C.). Nine herniae were found. These patients were then tabulated in the same way they had been when the study of pulmonary complications was made (Table I).

TABLE I
VITAMIN C AND POSTOPERATIVE HERNIA FOLLOWING BILIARY OPERATIONS

Preoperative Plasma Ascorbic Acid—Mg Per 100 Cc	Average Preoperative Diet in Mg Per Day			Total
	25	10-24	10	
0-5	$\frac{1}{11} = 9\%$	$\frac{0}{3} = 0\%$	$\frac{0}{0}$	$\frac{1}{14} = 7\%$
0.2-0.49	$\frac{1}{9} = 11\%$	$\frac{0}{11} = 0\%$	$\frac{1}{1} = 100\%$	$\frac{2}{21} = 9\%$
0.0-0.19	$\frac{1}{6} = 17\%$	$\frac{1}{6} = 17\%$	$\frac{2}{6} = 33\%$	$\frac{4}{18} = 22\%$
Unknown	$\frac{1}{2} = 50\%$	$\frac{0}{2} = 0\%$	$\frac{1}{1} = 100\%$	$\frac{2}{5} = 40\%$
Total	$\frac{4}{28} = 14\%$	$\frac{1}{22} = 5\%$	$\frac{4}{8} = 50\%$	$\frac{9}{58} = 15\%$

The numerators of each fraction indicate herniae. The denominators indicate total cases in each group.

It is seen from Table I that those cases with low plasma levels in the blood preoperatively showed a larger percentage of herniae than did those with high levels. Likewise, those with small amounts of the vitamin in their diet had a larger percentage than did those with fair or large amounts. However, these statistics, while we believe them to be of some significance, must be interpreted with great caution because of the fact that low plasma

values do not always mean depleted reserves, and patients who indicate a low intake on dietary history are perhaps not always telling the truth. However, *all* the patients in the higher brackets should heal, in so far as ascorbic acid is a factor in their healing. On the other hand, *some* of the patients in the lower brackets may be near enough to scurvy to interfere with their healing. With this reservation, and with the further reservation that the group of cases is small, it is believed that these statistics are sufficiently significant to indicate that cases with a low level of vitamin C in the plasma, if not corrected promptly, have more postoperative herniae than those with higher levels.

Disruption—Twelve cases of wound disruption have now been studied from the standpoint of surgical technic and vitamin C reserves. The study is much more detailed than that undertaken on the cases of herniae. The estimation of the reserve supply of vitamin C was not made by the same method in all instances, so each case will be discussed briefly. Very few cases were studied early in the work as we did not then know how to interpret our plasma vitamin C values in postoperative cases. No studies of plasma protein were made, but transfusions were administered freely in certain of the cases that would have been likely to have low plasma values.

The cases were operated upon by several different surgeons and various different technics of wound suture were employed. In all cases, catgut was used and in many cases the catgut was of much larger caliber (Nos 1 and 2

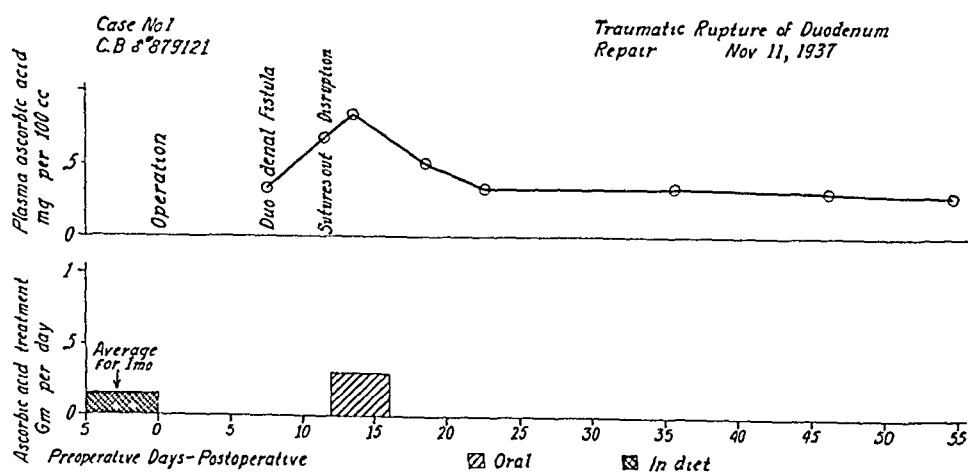


CHART 1

chromic) than recommended by Whipple. Layer suturing, continuous to the peritoneum, and continuous or interrupted to the fascia, and silk or silkworm gut in the skin was the technic in all cases. A few silkworm stay-sutures were introduced in all cases. No overlapping or mattress sutures were used in the fascia. This technic in no way meets the standards set up by Whipple or Harvey, but the incidence of disruption was not believed to be excessive, although statistical studies to determine this incidence were not made. Three cases in this series have already been presented and discussed¹⁵. They are Cases 2, 4, and 6. Case 2 of the previous report is not presented again as

the peritoneum did not separate. In this report, only cases with complete separation of all layers are considered. The cases are presented in chronological order.

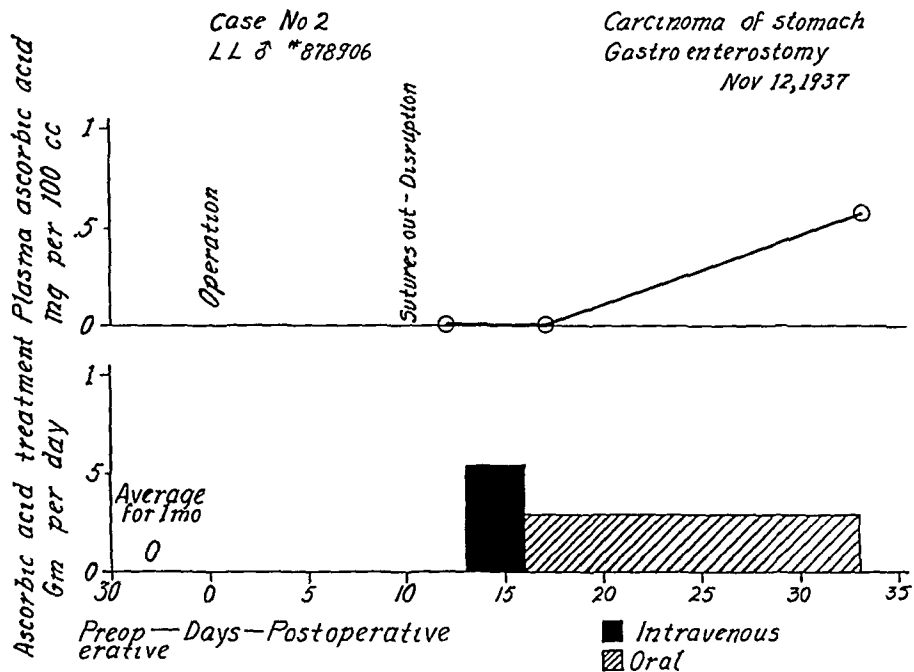


CHART 2

Case 1—No Scurvy Hosp No 879121 C B, a healthy high school boy, was injured playing football. He was brought to the hospital at once, and, at immediate operation, a traumatic retroperitoneal rupture of the duodenum was repaired with catgut. He had a stormy convalescence complicated by the early development of a duodenal fistula. Disruption occurred on the twelfth day, immediately after removing the stay-sutures. The wound was resutured. Chart 1 shows the intake and levels of plasma ascorbic acid. Calculations of the amount of ascorbic acid in the diet while in the hospital were not made as there was no possibility that this boy had scurvy. (See the high normal dietary intake before the accident.)

COMMENT—Because of the high dietary intake and the plasma levels well above zero, we do not believe that vitamin C had anything to do with the disruption. Treatment of 0.3 Gm per day was given because we did not then know that the levels determined were of no importance under these conditions. This disruption was due to technical factors and the chemical effect of duodenal secretion on the sutures. The boy eventually recovered.

Case 2—Near Scurvy Hosp No 878906 L L, male, age, 59, had carcinoma of the stomach. His diet had contained very little, if any, ascorbic acid for months and he had lost 50 lbs in weight. An exploration and anterior gastro-enterostomy were undertaken. Disruption occurred on the tenth day, shortly after removal of the stay-sutures. The wound was resutured and healed well.

COMMENT—The preoperative diet was such that a condition close to scurvy was likely. After four days of 0.6 Gm of ascorbic acid, intravenously,

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the plasma level was still zero After 17 further days of treatment by mouth, with daily doses of 0.3 Gm, the level was only 0.6 mg per 100 cc Inasmuch as there was no fever, sepsis or gastro-intestinal disturbance, these figures can only mean that this man probably had ascorbic acid deficiency of severe enough degree to contribute to this disruption

Case 3—No Scurvy Hosp No 932411 T A D, male, age 45, with a gastro-jejunal ulcer of considerable duration Vitamin deficiency was suspected and the ascorbic acid deficiency treated preoperatively, by giving 1.0 Gm per day for three days Determinations on two days showed a normal level A difficult gastric resection and

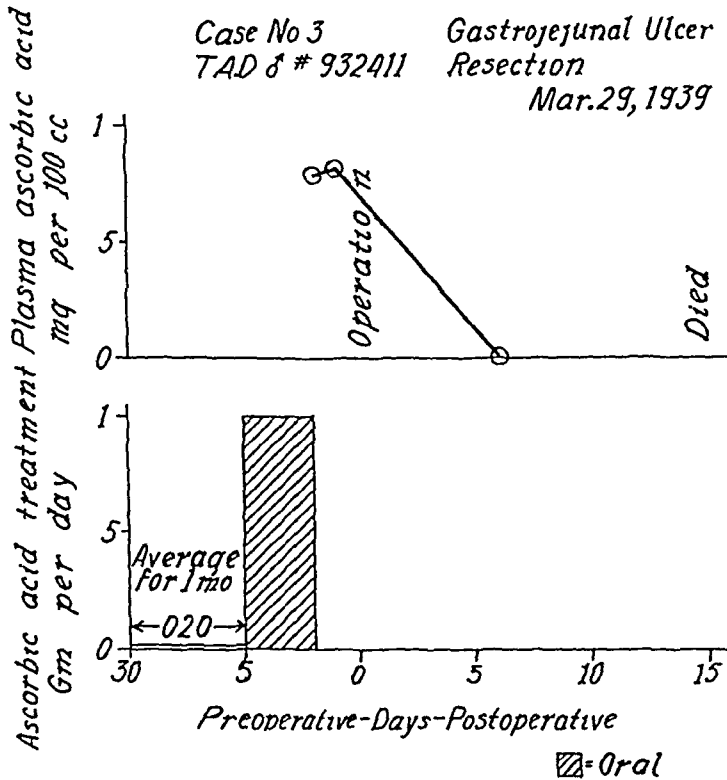


CHART 3

repair was performed On the third day, there was noted severe wound sepsis Other complications followed, including hemorrhages from the wound and the stomach Some delay occurred before treatment with vitamin K was given, as we did not, at that time, suspect that this deficiency was possible in such a case In spite of treatment with vitamin K and many transfusions, the man died of peritonitis Autopsy showed complete separation of the wound with a loop of intestine presenting just below the separated skin

COMMENT—Vitamin C played no part in this disruption, which was probably due, mainly, to effects of infection on the catgut sutures

Case 4—Probably No Scurvy Hosp No 939296 R F, male, had an appendix abscess Until ten days before admission, and 20 days before operation he had had a diet fairly adequate in ascorbic acid (about 40 mg a day) The operation consisted of drainage of the abscess through a right rectus incision Disruption and protrusion of loops of intestine occurred 33 days after operation

The data concerning vitamin C is relatively scanty Two days before the operation,

and on the fifteenth day after it, the plasma level was zero. No vitamin C was given before the disruption. The convalescence was very stormy. Practically no food was taken for three weeks after the operation during which time Wangenstein drainage was constant. Fever was present from before admission to after the disruption. Eventually he recovered.

COMMENT—No studies, that we know of, allow us to predict how long it takes for scurvy to develop in the presence of severe infection. All the evidence points toward the time being much shorter than without infection. The main cause of this accident was undoubtedly sepsis. Usually, in such cases

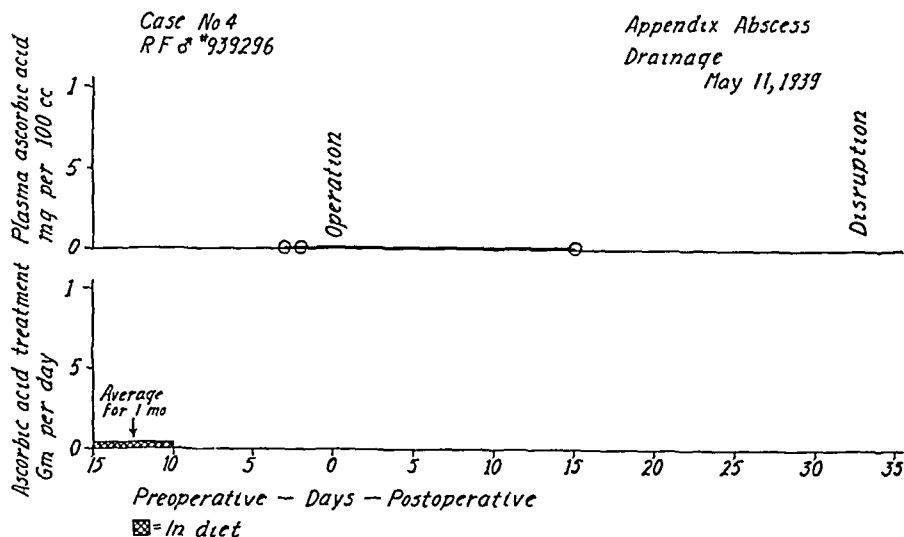


CHART 4

firm adhesions prevent protrusion of the intestines, even if the wound breaks down. Possibly, there was a factor of vitamin C deficiency developing late in the infection, but the conservative position to take is that this case probably suffered from no important deficiency in spite of the zero plasma levels.

Case 5—No Scurvy Hosp No 944466 M T, a male, had a ruptured gastric ulcer and was operated upon promptly. On the tenth day, the stay-sutures were removed and his wound disrupted a few hours later. Four days later, his ascorbic acid level was found to be 0.1 mg per 100 cc. The morning after the first dose of 1 Gm of ascorbic acid the level was 0.4 mg.

Comment—This finding indicates that vitamin C was not a factor in this case of disruption.

Case 6—Near Scurvy Hosp No 970288 M A had had a duodenal ulcer for a long time, and severe obstruction for months. He had also been a heavy user of alcohol. He had been able to retain very little of the nourishment taken by mouth for some time before operation and he had lost 50 lbs in weight. The surgical service had understood that plenty of ascorbic acid had been given before the operation, as preparation for it, but nobody realized how completely all food and vitamins taken by mouth had been vomited.

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After operation, his stay-sutures were removed prematurely on the sixth day. The wound promptly disrupted. No tablets of ascorbic acid were used, but from the second day after the disruption over a pint of orange juice was taken daily along with his food and he retained it all. This was equivalent to about 200 mg per day. The laboratory

Case No 5
M T ♂ #944466

Perforated Gastric Ulcer
Suture—June 21, 1939

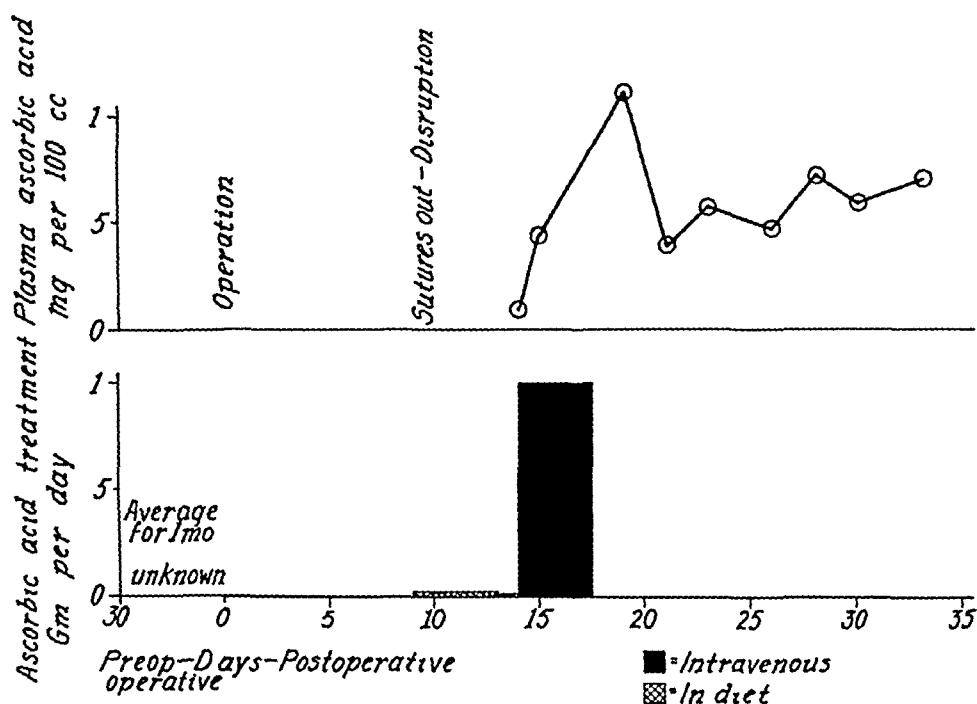


CHART 5

Case No 6
M A ♂ #970288

Obstructing Duodenal Ulcer
Gastro-enterostomy—Feb 23, 1940

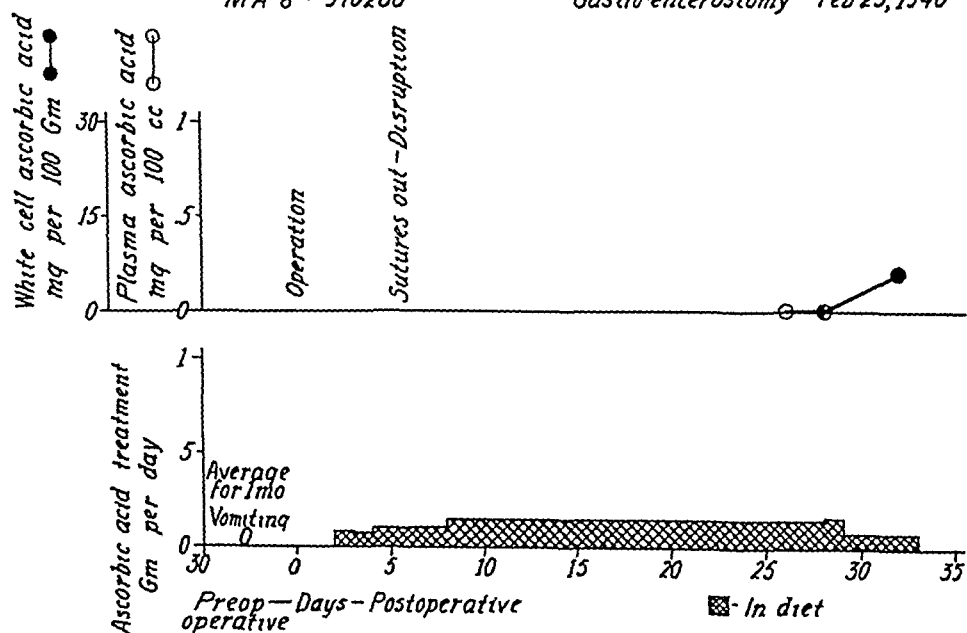


CHART 6

did not have an opportunity to determine the blood levels until after 22 days of high orange juice diet. Even at this time the plasma and white blood cell levels were extremely low.

Comment—This evidence points to a dangerous degree of scurvy. However, the removal of stay-sutures on the sixth day was inexcusable. The treatment of a man who vomits all his food should be by intravenous route.

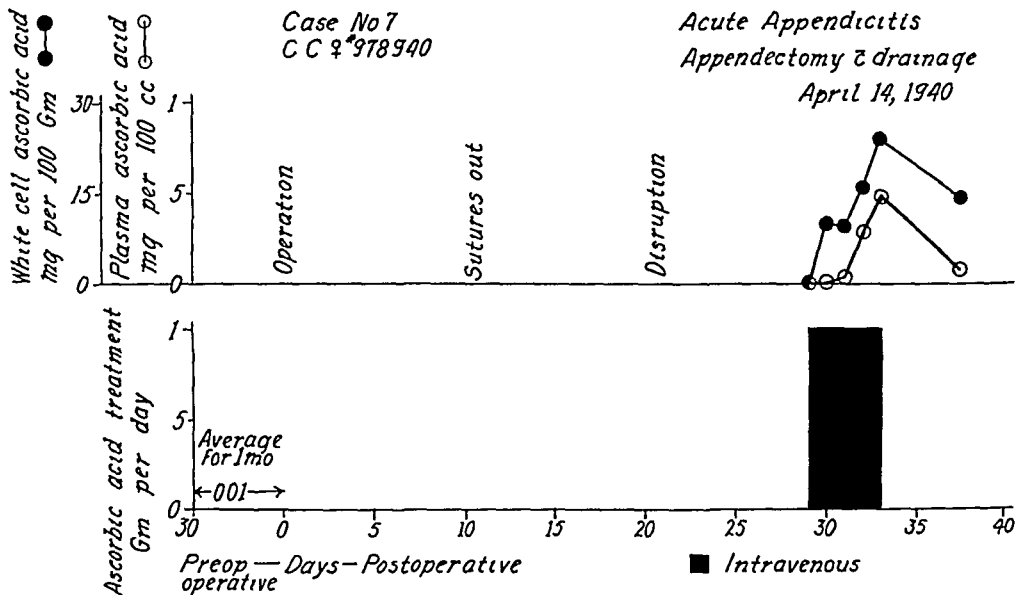


CHART 7

Case 7—Near Scurvy Hosp No 978940 C C, female, had acute appendicitis with peritonitis. Her diet before the illness had been very low in ascorbic acid containing foods. At operation, the appendix was removed, and the base of the cecum and the pelvis were drained. Stay-sutures were removed on the tenth day. The wound was moderately septic, and the patient was quite ill. Food was not taken well and no ascorbic acid given. On the twentieth day, a loop of intestine presented in the wound. This was replaced and held in by packing and strapping. Nine days later the patient was studied for scurvy and both the plasma and white cell levels were zero. The curve following the treatment proves a severe grade of deficiency.

Comment—There can be little doubt that scurvy played a part in this late disruption.

Case 8—No Scurvy Hosp No 981871 C B, male, had a subacute cholecystitis and a chronic gastric ulcer. His diet contained a small amount (about 12 mg of vitamin C) before entering the hospital. At operation the gallbladder was drained. The stay-sutures were removed on the eighth day, and he promptly disrupted. His wound was resutured. Some days later, the first vitamin C determinations showed none in the plasma, but about 6 mg, per 100 Gm in the leukocytes. After test doses the levels rose rapidly.

Comment—This evidence indicates that scurvy was not present.

Case 9—No Scurvy Hosp No 986160 E McN, male, young, had a traumatic rupture of the intestine, this time of the jejunum. His history showed a small intake of

WOUND HEALING

ascorbic acid before the injury His stay-sutures were removed on the tenth day and he disrupted He was resutured Vitamin C determinations showed zero in the plasma and 12 mg per 100 Gm in the leukocytes The test dose showed a rapid rise in both levels

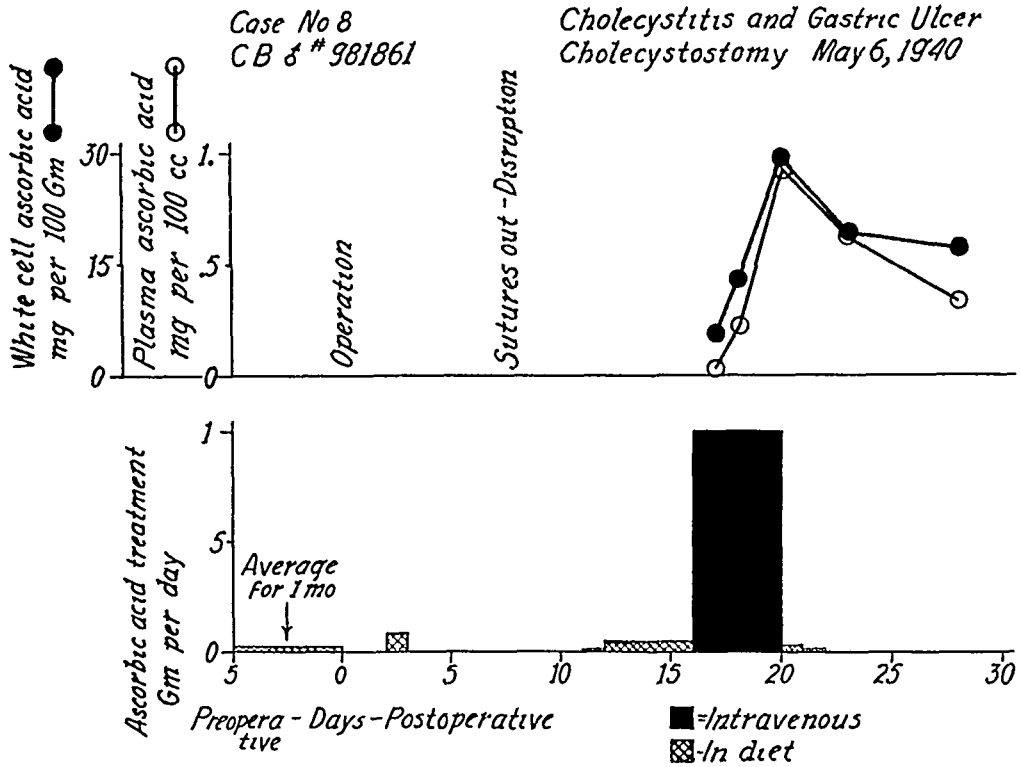


CHART 8

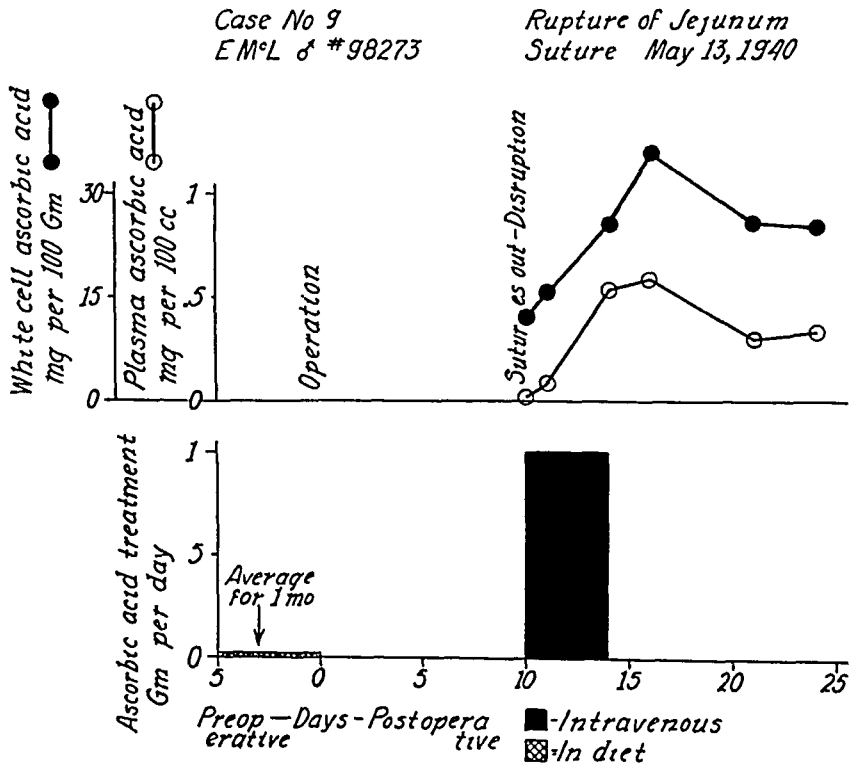


CHART 9

Comment—This finding, plus the response to test doses, proves the absence of scurvy

Case 10—*No Scurvy* Hosp No 982674 J M, male, had an obstructing duodenal ulcer Although his preoperative leukocyte ascorbic acid was 14, he was given treatment intravenously with the results to the plasma and leukocyte levels shown on the chart On the tenth day postoperatively the stay-sutures were removed and there was a small disruption This was controlled by packing and strapping

Comment—Scurvy could have had no part in this accident

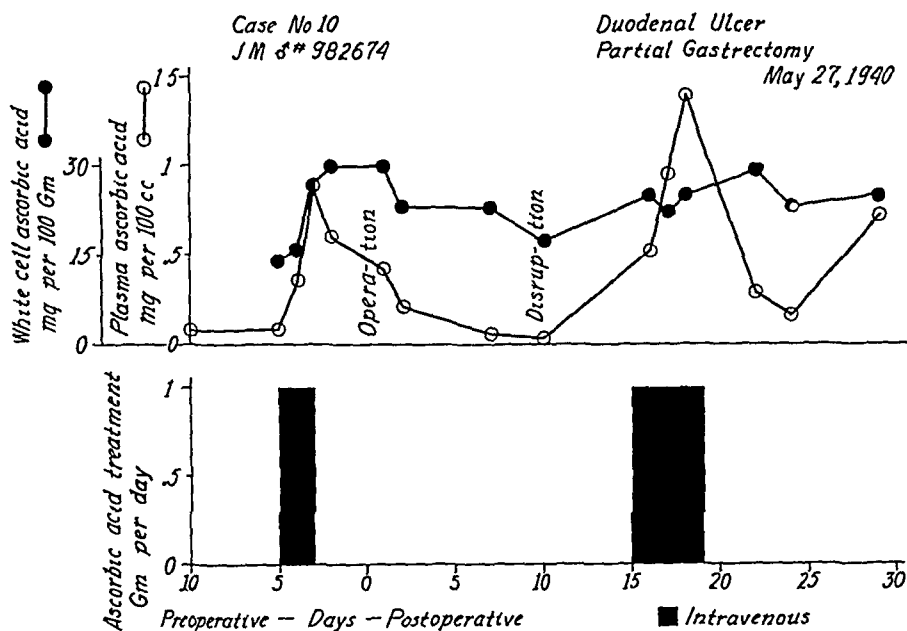


CHART 10

Case 11—*No Scurvy* Hosp No 985945 P B, male, rather feeble, with carcinoma of the sigmoid He took a small amount of vitamin C in his food before operation On the tenth day, his sutures were removed and he disrupted His leukocyte level was eight He was resutured and given vitamin C, but he died the next morning

Comment—With this leukocyte level the man could not have had a severe enough deficiency for it to be a factor in this disruption

Case 12—*No Scurvy* Hosp No 995658 T E had a partial gastrectomy for duodenal ulcer His preoperative diet had contained a small amount of vitamin C On the sixth day, the stay-sutures were removed and the wound disrupted It was resutured The 0.5 Gm doses of ascorbic acid were given for three days, after which the leukocyte level was 25 mg per 100 Gm, and the plasma level 0.04 mg per 100 cc

Comment—It is believed that the level of 25 mg in the leukocytes, after only 1.5 Gm of treatment, indicates that the wound was not affected by lack of vitamin C

Discussion—Twelve cases of disruption of abdominal wounds have been studied Scurvy played no part in the accident in Cases 1, 3, 5, 8, 9, 10, 11, and 12 This statement is made in spite of the fact that most of these cases

had very low plasma vitamin C levels, at one time or another, during their illness. Cases 2, 6, and 7, had a severe depletion of their vitamin C reserves, and scurvy probably delayed, or prevented, the healing of their wounds (Case 4 is doubtful).

In none of the cases was the method of suturing up to the standards of technic set up by Whipple. On the other hand, it must be stated that these disruptions occurred among a very large number of abdominal operations,

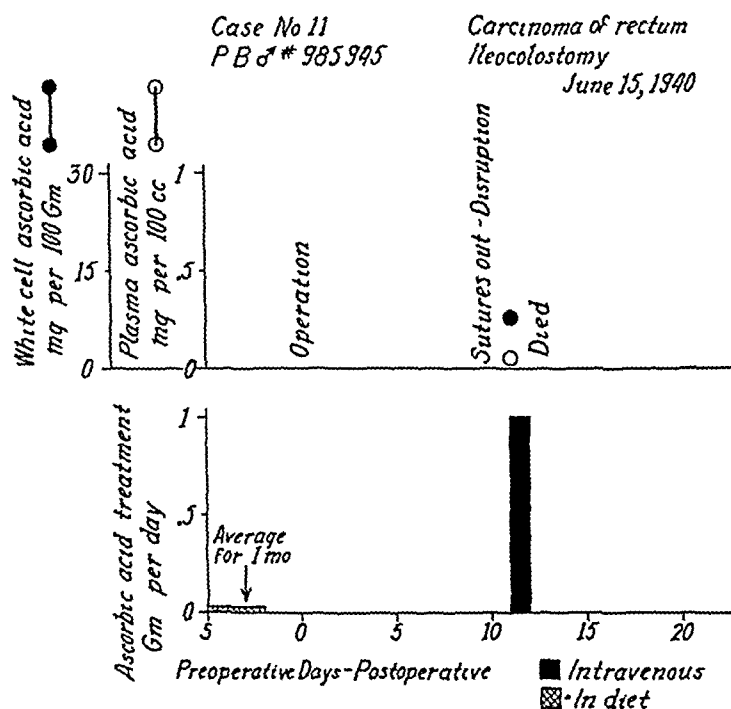


CHART 11

and the percentage of these accidents is low, showing that the methods of suturing used were, at least, reasonably good. Stay-sutures were used in all cases, and in some cases were removed much too early. If stay-sutures are put in for a purpose, the purpose must be to support the wound until natural healing has taken place sufficiently to make their presence superfluous. This makes it imperative that they remain, at least, until the twelfth or the fourteenth day.

It is obvious from the cases presented that a larger part of the problem of disruption will be solved by improved technic than by studies of or treatment with vitamin C. On the other hand, the fact that a few cases of disruption occur in patients with severe depletion of the vitamin C reserves, indicates that these reserves should be studied before operation. A series of gastric and duodenal ulcer patients who were in the hospital at the same time as those cases reported here, are also being studied and will be reported in another communication. Several of them had deficiencies comparable to that of Case 7, above. However, their deficiencies were corrected either just before or just after operation. If they had not been treated, the number of

cases disrupting from ascorbic acid deficiency might have been larger. Most surgical services have no facilities for such studies and such studies are extremely expensive. The authors are convinced that wide installation of such facilities are not necessary at present. In another communication, we hope, shortly, to prove that a few minutes spent in securing and analyzing a short dietary history will do as much or more to determine these reserves than ascorbic acid determinations. In such a history, special attention should be given to the amounts of certain foods that are eaten per day. About

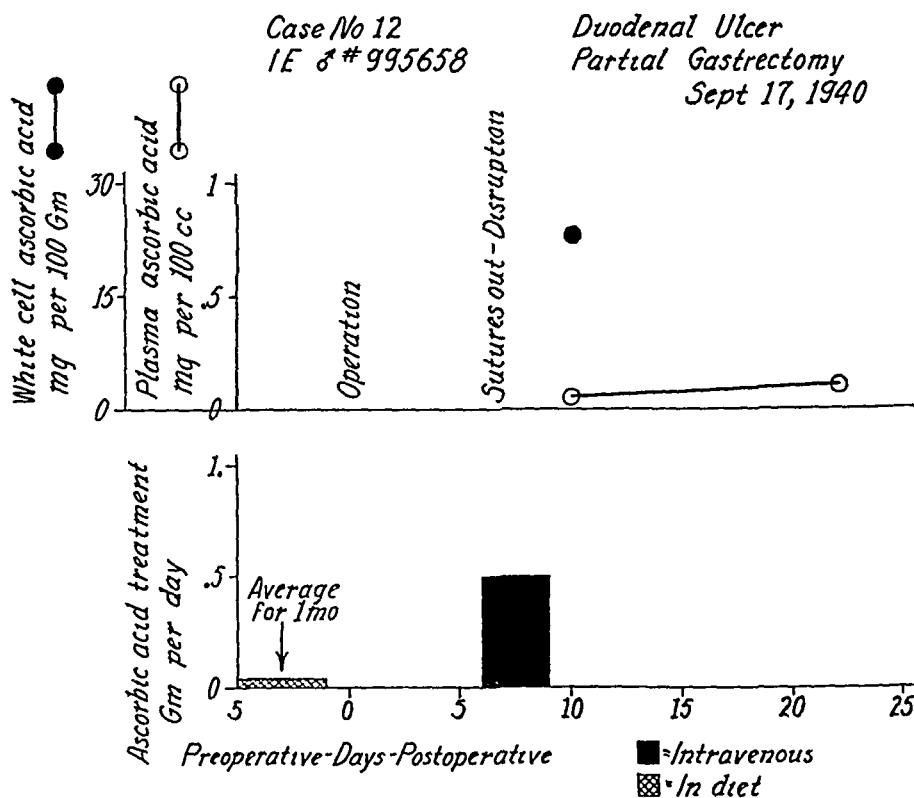


CHART 12

75 mg of ascorbic acid is generally accepted as an amount that will keep a well person saturated. We believe that even 20 mg will keep sufficient reserves so that wounds will heal easily and well. Seventy-five mg will be furnished by the amounts of food shown in Table II. Many other foods have

TABLE II

AMOUNTS OF CERTAIN FOODS NEEDED DAILY TO FURNISH 75 MG OF ASCORBIC ACID
IF THE PARTICULAR FOOD IS THE ONLY SOURCE OF THE VITAMIN

Fresh citrus fruit or juice and fresh strawberries	150 Gm or cc
Canned citrus fruit	250 Gm or cc
Fresh or canned tomatoes or tomato juice	300 Gm or cc
Cooked liver	300 Gm
Cooked potatoes (except fried)	300 Gm
Raw apples, pears, other fruits and berries	1-5 Kg

Lettuces, other greens, and most vegetables contain small amounts, and part of these small amounts may survive cooking.

small amounts of this vitamin, but grains and flour have none, and pasteurized milk very little

Full data of this nature has been presented by Daniel, and Munsell,²¹ and by many other students of diet

Following the securing of data from the diet, those patients with very low reserves should be treated. The treatment should be given preoperatively in an "elective" case, and immediately postoperatively in an "emergency" case. Ascorbic acid is cheap and may be given by mouth, intramuscularly or intravenously (using different preparations). About 4 Gm are needed to bring a severe case of scurvy up to saturation. This may safely be given in four days. Be sure, however, that the treatment be intramuscular or intravenous if there is likely to be vomiting or diarrhea, otherwise it makes no difference which way it is given.

SUMMARY AND CONCLUSIONS

(1) A study of preoperative diet and preoperative plasma vitamin C levels of patients having operations upon the biliary tract was made

(2) Those with poor intake or low levels or both, had a higher percentage of postoperative hemiae than those with better intakes or levels

(3) A study of 12 cases of abdominal wound disruption shows that mechanical factors were more frequently the determining ones for disruption than depletion of vitamin C reserves in this series

(4) Three cases, however, had sufficient degrees of ascorbic acid deficiency, so that this was an important factor in their disruptions. In a fourth case, depletion to a dangerously low level may have taken place, but the data are too incomplete to be sure

(5) Two cases of depleted reserves were associated with lesions of the stomach, and two (including the doubtful one) with appendicitis

(6) These studies indicate a need for improvement in surgical technic, and for routine study of vitamin C reserves by surgeons

(7) Study of vitamin C reserves may be made by means of dietary histories and should be followed by preoperative, or early postoperative treatment of the few patients that probably have low reserves

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THE EFFECT OF THE LOCAL AND ORAL ADMINISTRATION OF COD LIVER OIL ON THE RATE OF WOUND HEALING IN VITAMIN A-DEFICIENT AND NORMAL RATS *

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IN A previous paper,¹ we reported that the topical application of cod liver oil healed ulcers of the lower extremity of diabetic patients more effectively than a controlled group who were not thus treated. In an effort to determine more accurately the effect of cod liver oil on the rate of healing of wounds, the following study was undertaken.

Cod liver oil has been used locally in the healing of wounds and burns in patients since 1934.²⁻⁷ All observers report an increase in the rate of wound healing and a decrease in the severity of infection when present. Experimentally, Kemmler,⁷ Píoto,⁸ and Lohr and Unger,⁹ have studied the effects of cod liver oil upon rabbits and guinea-pigs, and have found it effective in accelerating wound healing. There are three factors in cod liver oil which might be responsible for its healing effect. These are vitamins A and D and the unsaturated fatty acids. Vitamin D is concerned principally with the metabolism of calcium, and, unless the wounds involved the bony structures, or the animals were on diets deficient in calcium or vitamin D, the effect on the healing of wounds involving epithelial structures would be slight, if any. Vitamin A, on the other hand, is known to affect the epithelial tissues, and a deficiency of this vitamin results in hyperkeratinization of the epithelium. The unsaturated fatty acids are concerned with the condition of the skin, and in animals deprived of linolic or linolenic acids¹⁰ dryness and scalliness of the skin occurs.

In the present study, we are reporting the effects of cod liver oil and linseed oil, applied locally, on the rate of wound healing in rats. In addition, one group of vitamin A-deficient rats were fed an equivalent amount of cod liver oil to find out if the parenteral administration was as effective in healing the wounds as was the direct local application of the vitamin. Both normal and vitamin A-deficient rats were used in order to compare the rate of healing in entirely normal animals with the rate of healing in the deficient animals.

Procedure—All the rats were bred in this laboratory from an original Wistar strain, and the experiments were made on litter mates.

The normal rats consisted of litters fed the laboratory stock diet of which the vitamin A content was 245 IU per 100 Gm. They were wounded at the same age as the vitamin A-deficient rats, which was the time at which

* This data was included in a thesis by Dr. Harold Brandaleone for the Degree of Doctor of Medical Science in New York University, New York, N. Y.

the latter developed the signs of vitamin A deficiency, and was at an average age of 107 days. When wounded, the normal animals were divided into two groups, Group B—in which the wounds were allowed to heal without treatment of any kind, and Group D—in which the wounds were treated with cod liver oil.

The animals which were to be depleted of their vitamin A stores were started on the vitamin A-deficient diet when age 27 to 37 days. The diet consisted of casein 9.61 per cent, salt mixture 3.85 per cent, sodium chloride 0.96 per cent, dried brewer's yeast 9.61 per cent, cornstarch 56.75 per cent, Cusco 19.22 per cent, and 0.3 Gm of viosterol was added to 1,000 Gm of this mixture. The animals were allowed to eat the diet *ad lib*. When the symptoms of the deficiency began to occur, the rats were wounded. Four groups of animals were studied on the vitamin A-deficient diet: Group A—in which no local treatment of any kind was used on the wounds, Group C—in which cod liver oil was applied to the wounds, Group G—in which the wounds were treated with unboiled linseed oil, the iodine number of which was 158, and Group H—in which the wounds were not treated but the rats were fed the same amount of cod liver oil as was applied locally to the wounds of the animals in Group C (Table I).

TABLE I
STATUS OF THE GROUPS OF RATS STUDIED

Group	No of Rats	Mortality	Infection	Condition of Animals and Treatment of Wounds
A (1 and 2)	62	60%	22%	Rats were fed diet deficient in vitamin A. Wounds were untreated. The diet of the parents of A ₁ was higher in vitamin A than the diets of the parents of A ₂ .
C	52	0	0	Rats were fed diet deficient in vitamin A. Wounds were treated with cod liver oil.
G	49	41%	10%	Rats fed diet deficient in vitamin A. Wounds were treated with unboiled linseed oil (iodine number 158).
H	29	0	0	Rats fed vitamin A deficient diet. Wounds were untreated. Cod liver oil fed by mouth.
B (1 and 2)	45	0	5%	Rats were normal. Wounds were untreated. B ₁ rats were 19 days older at the time of wounding than rats in B ₂ group.
D	40	0	0	Rats were normal. Wounds were treated with cod liver oil.

The animals on the vitamin A-deficient diets were wounded at the time when they failed to show any increase in weight for a period of seven days. This was before any other pronounced symptoms of vitamin A deficiency had appeared, for we found that, if wounding was delayed longer, the rats died soon after the wounds were made.

Manner of Wounding and Method of Measuring Wounds—All the rats were wounded as follows. The hair over the thoracic vertebrae was clipped, the skin shaved clean and grasped with a pair of forceps, and an elliptical wound extending through subcutaneous tissues was made with a pair of scissors. An impression of the shape of each wound was taken by placing a piece of filter paper over the fresh wound. The wound was not measured

until the day after it was made, in order to obviate any error due to the stretching of the skin which occurred immediately after wounding. The long and wide diameters were measured in centimeters with calipers. Measurements were taken two or three times a week until the wound was completely healed, or the animal died. In the latter case, the diameter of the wound at the time of death was measured. The calculations of the total area in each wound was elliptical in shape. This formula is $\frac{\pi}{4} \times a \times b = \frac{3.14}{4} \times a \times b = 0.785 \times a \times b$. In order to prevent the animal from licking or scratching the wound a metal cap approximately 2 cm in height and 2.5 cm in diameter was shaped to the back of the animal and attached with adhesive tape wrapped around the abdomen. The oils were dropped on the wound from a measured dropper. Enough oil was applied to just cover the wound, from two to four drops at first, and, as the wound became smaller, one drop. The amount of vitamin A was calculated from the total number of drops of cod liver oil used. Treatment with cod liver oil or linseed oil was begun 24 hours after wounding and was repeated daily.*

At the end of the experiment, an average period of 20 days, the animals were anesthetized and exsanguinated. The wounded area was excised and preserved in 10 per cent formalin solution for histologic examination. The wound was considered healed when complete epithelium covered the wound and a white scar was present.

RESULTS ON THE RATE OF WOUND HEALING

(1) *In the Vitamin A-Deficient Rats (Groups A, C, G, and H)*

Group A (vitamin A-deficient rats whose wounds were *not treated* with any agent) —This group was subdivided into two parts (A_1 and A_2) because the parents of the rats in Group A_1 were on a higher vitamin A diet than the parents of the rats in Group A_2 . However, once the animals had become vitamin A-deficient the rate of wound healing was the same in all the animals. Group A_1 healed at the rate of 0.046 sq cm daily, Group A_2 at the rate of 0.045 sq cm daily. Calculated as a single group, the daily rate of healing was 0.045 sq cm \pm S D \pm 0.035 (Table II).

Group C (vitamin A-deficient rats whose wounds were *treated with cod liver oil*) —In this group the daily rate of healing was 0.088 sq cm with a standard deviation of \pm 0.027. This was significantly greater than in Group A, whose wounds were untreated.

The standard deviations were calculated from the formula¹¹ $S D = \sqrt{\frac{d^2}{n-1}}$. Comparing Groups A and C, the value for *E* is significant as shown in Table III.

* The cod liver oil was supplied by the Mead-Johnson Laboratories. The vitamin A content of the cod liver oil was 668 international units per gram.

† $S D = \text{Standard deviation} = \sqrt{\frac{d^2}{n-1}}$

Group H (vitamin A-deficient rats whose wounds were *untreated but who were fed cod liver oil*) —The average rate of healing in this group was 0.069 sq cm \pm S D 0.021. This rate of healing was significantly faster than in the untreated A-deficient rats but slower than in the wounds treated locally in the A-deficient rats.

TABLE II
EFFECT OF COD LIVER OIL ON THE DAILY RATE OF
WOUND HEALING IN NORMAL AND VITAMIN A DEFICIENT RATS†

Group	No of Rats	Condition of Rats	Daily Rate of Healing Sq Cm \pm S D *	Total U S P Units Contained in Cod Liver Oil Given	Weight Change from the Time of Wounding to Death
A	45	Vitamin A deficient No cod liver oil	0.045 \pm 0.035	None	-27 Gm
C	38	Vitamin A deficient Treated locally with cod liver oil	0.088 \pm 0.027	483	+16 Gm
G	37	Vitamin A deficient Treated locally with linseed oil	0.051 \pm 0.043	None†	-35 Gm
H	19	Vitamin A deficient Fed cod liver oil No local treatment to wound	0.069 \pm 0.021	358	+34 Gm
B	39	Normal rats No cod liver oil applied locally	0.082 \pm 0.025	None	+32 Gm
D	35	Normal rats Treated with cod liver oil locally	0.087 \pm 0.028	645	+ 6 Gm

$$* \text{ S D } = \text{ Standard deviation } = \sqrt{\frac{\sum d^2}{n-1}}$$

† Wounds treated with a total of 1.196 Gm of unboiled linseed oil

‡ This table includes all wounds whether completely or partially healed

Group G (vitamin A-deficient rats whose wounds were *treated with linseed oil*) —In this group the daily rate of healing was 0.051 sq cm \pm S D 0.043. This is not significantly different from Group A but is significantly different from Group C. The results with linseed oil indicate that these unsaturated fatty acids do not exert a healing effect.

(2) The Rate of Wound Healing in the Normal Rats (Groups B and D)

Both of these groups were absolutely normal rats, on entirely adequate diets. There was practically no difference in the rate of wound healing between Group B whose wounds were not treated with cod liver oil, and Group D, whose wounds were treated. The average daily rate of healing in Group B was 0.082 \pm S D 0.025, and in Group D 0.087 \pm S D 0.028 (Table II). Apparently, cod liver oil, applied locally to this type of wound in well-nourished normal rats, does not significantly affect the rate of wound healing.

The statistical comparisons of the rate of wound healing between the various groups is given in Table III. The differences between Groups A and C, C and G, C and H, A and H, and B and H are significant. According to Chaddock,¹¹ for the differences to be significant the value of E should be

TABLE III

COMPARISON OF VARIOUS GROUPS OF RATS WITH RESPECT TO DAILY RATE OF WOUND HEALING

Groups Compared	Difference between the Means (Sq. Cm./Day)	Probable Error of the Difference between the Means	E* = Difference Between Means—Probable Error of the Difference between the Means
A and C	0.043	0.0047	9.1
B and C	0.006	0.0041	1.5
B and D	0.005	0.0045	1.1
C and D	0.001	0.0048	0.2
A and G	0.006	0.0059	1.0
C and G	0.037	0.0056	6.6
C and H	0.010	0.0043	4.4
A and H	0.024	0.0047	5.1
B and H	0.013	0.0042	3.1

* E was calculated as the quotient of the difference between the means divided by the probable error of the difference. The validity of this measure is supported by the fact that the plotted data approximate a normal distribution curve.

above 2.5. Groups B, C and D are not statistically different. The rate of wound healing in the vitamin A-deficient rats treated with cod liver oil was approximately the same as the rate of wound healing in the two normal groups.

(3) Observations on the General Condition of the Animals in the Different Groups

In the vitamin A-deficient groups, A and G, receiving no cod liver oil locally, the symptoms of vitamin deficiency persisted after wounding. These symptoms included loss of weight, fur changes, anorexia, humpback, crusting of the nose and eyes, and xerophthalmia. The average loss of weight in these two groups was 32 Gm during the period of observation. In Group C, where the wounds were treated with cod liver oil, there was an average gain of 16 Gm during the experimental period. Although the symptoms of vitamin A deficiency persisted in some of the animals, they were much less severe and less frequent. This was not due to licking the oil off the wounds, as the metal caps placed on the wounds prevented the animal from reaching the wound with his paws or tongue. In the vitamin A-deficient rats fed cod liver oil (Group H) the symptoms of vitamin A deficiency were rapidly controlled, and these animals gained an average of 34 Gm during the period of observation. None of the animals died, and no infections occurred in the group.

In Group A, the wounds healed completely in only 18 of the 45 rats, the other rats died before healing was effected. Of the 18 wounds healed, four showed possible evidence of infection (*i.e.*, pus and necrosis), of the 27 wounds that healed partially, six showed gross evidence of infection. In Group H, all of the wounds healed completely. In Group B, all the wounds healed completely, and there was gross evidence of infection in two of them. In Group G, of 37 wounds, 22 healed completely and six showed gross evidence of infection.

In the wounds treated with cod liver oil, the edges were even, in contrast

to the irregular edges in the untreated wounds, profuse granulation tissue was evident, and epithelization occurred earlier than in the untreated group, and was more abundant. The wounds finally closed leaving a small, white scar.

Discussion—The absorption of certain vitamins through the skin has been established.¹⁵ Helmer and Jansen¹⁶ demonstrated that vitamin A, contained in halibut liver oil and carotene, is readily absorbed through the skin of rats, preventing the severe symptoms of vitamin A deficiency. Eddy and Howell¹⁷ demonstrated the absorption of vitamin A through the unbroken skin of rats. Judging from our results, the local application of cod liver oil to the wounds of vitamin A-deficient rats will increase the daily rate of healing and will improve the general nutritional state of the animals. The feeding of cod liver oil is not as effective in healing wounds as is the local application.

Just what factor in cod liver oil is responsible for the healing effect remains to be determined. Apparently, it is not the unsaturated fatty acids, as linseed oil contains large amounts of the unsaturated fatty acids, with the exception of arachidonic acid. Getz,¹² working on tuberculous ulcers in guinea-pigs, has shown that the healing agent in cod liver oil is contained in the "vitamin fraction." He also reports that more rapid healing did not occur when fish oils with higher concentrations of vitamins A and D were used. If vitamins A and D were the only factors responsible, one might expect that the rapidity of the healing process would parallel the increased concentration of the vitamins. As there is, undoubtedly, a limit to the rapidity with which healing can occur, and, as this may have been reached at the lower concentration of the vitamins, such a correlation between the rate of healing and the concentration of the vitamins may not hold. The majority of investigators agree with Getz that the unsaponifiable or "vitamin fraction" of cod liver oil contains the healing agent. Up to the present time, no other single factor has been isolated.

In our *normal* animals, the local application of cod liver oil had no significant effect on the rate of healing. There might seem to be some discrepancy in this respect between our results and those of other observers, who report beneficial effects from the application of cod liver oil to burns,¹³ and in tuberculous lesions in normal animals,¹⁴ and in crushing wounds and burns in animals.^{2a} In this study, the normal animals were in an optimal state of nutrition, and the wounds were made with as little trauma as possible, so that there was no injury to the deep tissues. The types of wounds in which cod liver oil has been effective in patients have been traumatic, *e g*, crushing wounds or burns, or wounds secondary to a metabolic disorder.^{1, 2, 3, 4, 6, 8} and the nutritional status of the patients probably was not optimal. In these normals, the rate of healing that occurred represents the normal rate, and as far as we know at the present time, the maximum rate of healing. It may be that this rate of healing can be further increased by some more potent agent but, obviously, a point will be reached at which no further increase in the rate of healing can occur.

Drigalski¹⁴ found that cod liver oil had a definite bacteriostatic as well as bactericidal action, and believes that it tends to hinder the passage of toxins from wounds into adjacent tissue. In our series, no infections occurred in the wounds in either the normal or vitamin A-deficient animals treated with cod liver oil or fed with it. No special precautions were taken in any of the animals to avoid infection. In the normal animals whose wounds were not treated with cod liver oil, there was evidence of infection in two of them. The incidence of infection in the vitamin A-deficient untreated groups was quite definite, averaging 20 per cent. Sixty per cent of the animals in this group died before complete healing had occurred.

It is particularly interesting to note that the local application of cod liver oil was more effective in increasing the daily rate of healing than was the feeding of cod liver oil. The effect of the local application, apparently, is a direct as well as a general one, as the nutritional state of these animals was also improved.

Calculation of the total number of days required for complete healing of wounds in the various groups could not be satisfactorily evaluated. First, because in the A-deficient group some of the animals died before complete healing occurred. Secondly, the exact end-point of healing could not be determined to the hour at which it occurred, and it was, therefore, difficult to calculate the total number of days and hours required for complete healing. Obviously, a time interval of 24 hours becomes too large a unit for the accurate estimation of the healing of wounds of small dimensions.

CONCLUSIONS

(1) The daily rate of healing in experimentally wounded vitamin A-deficient rats was accelerated by the direct application of cod liver oil to the wounds. The direct application of cod liver oil did not increase the daily rate of wound healing in normal rats.

(2) Linseed oil, directly applied to the wounds, did not significantly increase the daily rate of healing in vitamin A-deficient rats.

(3) The feeding of cod liver oil increased the daily rate of healing in the vitamin A-deficient rats but not to as great a degree as did the local application of cod liver oil.

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BRIEF COMMUNICATION

TABLE TOP FOR ROENTGENOGRAPHY, ESPECIALLY OF THE BILIARY TRACT, DURING OPERATION

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ROENTGENOGRAPHY during operation has found certain limited applications, as for example in bone operations, search for foreign body, exploration of biliary ducts, and combined instrumental and roentgenographic examination of the uterine cavity. When its technic has been simplified, as in examination of the exposed kidney, it has become popular. But clumsiness of method has retarded most of its potential uses. Sliding a cassette either directly beneath the patient or into a "tunnel" opening at the side of the

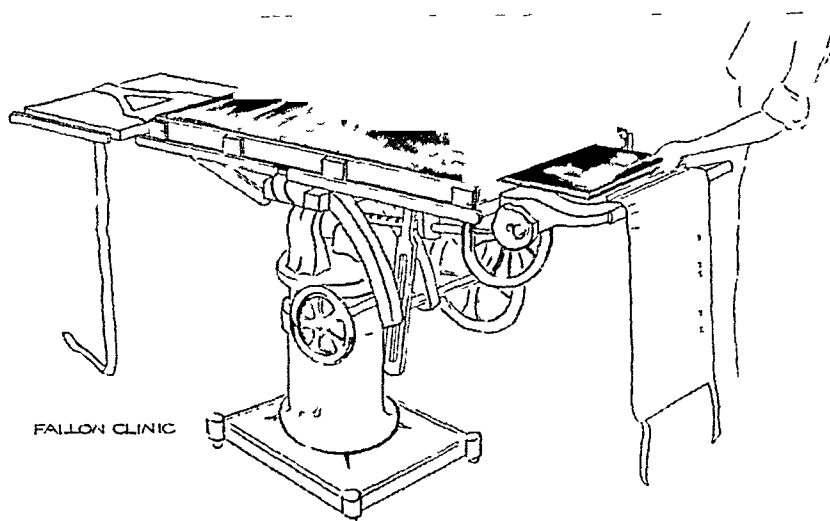


FIG 1—Roentgenographic overtop. The cassette is maneuvered from the ends of the table without disturbing the operation.

operating table disrupts the sequence of the operation, distracts the operating team and jeopardizes sterility. But a space beneath the patient, opening at the ends rather than at the side of the table, would allow manipulating the cassette without disturbing patient, drapes or team.

Such an end-opening space is provided by an overtop* made of one-eighth-inch (3 Mm) "Masonite," a wood composition chosen as the least radiopaque of several materials tested, resting upon metal side walls which lock into the side-rails of the table. It replaces those sections of the cushion

* Manufactured by the Scanlan-Morris Co, Madison, Wis

under the torso. Beneath the overtop, on the top of the table, slides a wide canvas belt with a frame to hold the cassette. One end of this belt leads over the head of the table and from the other a strap leads to its foot. By these the cassette may be pulled either sidewise or to-and-fro by the roentgenologist and anesthetist, standing at opposite ends of the table, and well away from the operating area. Inserting a fresh cassette involves only lifting the patient's head. A yardstick held beside the patient shows how far from the end of the table the cassette should be, and an inch scale printed on the belt shows how far from the end it is. A large film (14×17 inches, 35×43 cm) gives latitude in aiming the rays. A Lysholm grid substitutes for a Bucky. The grid is light and thin, moves with the cassette and obviates a mechanism for tripping a Bucky.

To permit holding the breath, spinal anesthesia is advisable for some roentgenograms, especially cholangiograms. Ordinarily, the operator covers the patient with a large sterile sheet on which he marks the center of the field with a dab of blood, then steps back to give place for the portable roentgen unit, while the assistants hold their retraction.

In calculating exposure, therefore, the roentgenologist must allow for the tissues retracted out of the path of the rays. Exposure factors for a cholangiogram with brominized oil are 75–88 Kv, ten Ma, 17 inch (43 cm) distance, one second, cone five inches (13 cm) in diameter and six inches (15 cm) long, superspeed intensifying screen. If a Lysholm grid is used—we usually have found it unnecessary—the exposure is three seconds. Film development time may be cut to a minute by quick developers, such as a modification of their D-8 formula obtainable from the Eastman Kodak Co.

Four years' use of this apparatus has disclosed two disadvantages. The thin top sags beneath extremely heavy patients. But we nevertheless prefer it to a thicker top, because these are just the patients who need the least possible added opacity. Secondly, the absence of a cushion increases the incidence of postoperative backache, so the apparatus should not be used routinely but only when it is likely to help.

Figures 9 and 10 in the article on "Surgical Problems of War," by Mr. L. R. Broster, in the June, 1941, ANNALS OF SURGERY, in addition to the acknowledgment to the Royal Society of Medicine should have carried credit to Dr. E. G. L. Bywaters and Dr. D. Beall.

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THE PROPHYLAXIS OF PULMONARY EMBOLISM BY DIVISION OF THE FEMORAL VEIN

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THE PURPOSE of this communication is to offer evidence that division of the femoral vein is advisable as a *routine* prophylactic measure against pulmonary embolism when thrombosis of the deep veins of the lower leg is present or suspected *

The common impression that a pulmonary embolus is an unavoidable accident is no longer tenable. Available evidence demonstrates that the site of origin of the thrombus responsible for the pulmonary embolus is, as a rule, not in such inaccessible areas as the iliac and pelvic veins, but rather in the veins below the common femoral and, primarily, in the veins below the knee. In 133 cases of venous thrombosis, Frykholm¹ by anatomic dissection found the following distribution: Eighty-five (64%) were located in the popliteal vein or its branches, four (3%) in the femoral vein distal to the vena profunda, 25 (18%) in the vena profunda or its branches, four (3%) in the common femoral, two (15%) in the iliac veins, and eight (6%) in the deep pelvic veins. It is, therefore, clear that in 85 per cent of Frykholm's cases of venous thrombosis the process was distal to the entrance of the profunda, *i e*, in the femoral vein and, primarily, in its branches below the knee.

Neuman,² in an unselected series of 165 patients, dead of a variety of diseases, surgical and otherwise, studied the veins of the leg by dissection of the plantar and thigh veins and by serial sections at 2 cm intervals along the veins of the lower leg. Venous thrombosis was found in 100

* It should be clear that we are not concerned in this paper with pulmonary embolism arising from auricular fibrillation or any vascular disorder of the venous system cephalad to the great veins in the pelvis.

cases, in 52 per cent the process was bilateral. Thrombosis in the veins of the thigh was present in 45 per cent, but in every instance only as a continuation of a more distal thrombosis and never as an isolated process—an observation recently confirmed in the living subject by Bauer¹⁰. Neuman demonstrated the segmental distribution of the thrombosis, with intervals of freedom at those points in the lower extremity where compression by extra-venous structures is likely. Thrombosis, solely in the plantar veins, was equally distributed among all decades from 20 to 80 years of age, thrombosis, solely in the deep veins of the calf, increased in frequency with age. Neuman considers thrombosis in the plantar veins a more malignant type because it gave evidence of a greater predisposition toward rapid propagation of the clot into the veins of the thigh. Twelve per cent of cases with thrombosis showed massive pulmonary emboli. An additional 34 per cent showed multiple nonfatal emboli.

Roessle³ found thrombosis in the deep veins of the calf in 88 of 324 routine autopsies in adults over 20 years of age. Of these, 38 showed, in addition, thrombosis in the femoral veins. Ten cases showed massive pulmonary emboli arising from the femoral vein, in all of which there was an associated thrombosis in the calf veins.

In a statistical study of 897 cases of fatal and nonfatal embolism by Barker, *et al*,⁴ 45 per cent were said to have shown no clinical or necropsy evidence of venous thrombosis. The absence of clinical evidence is notoriously unreliable because thrombosis is often not demonstrable by prevailing clinical methods. The absence of necropsy evidence cannot be accepted as proved, because the examination did not include a dissection of the veins in the lower thigh and lower leg.⁵

Of a total of 1,401 cases of postoperative thrombophlebitis reported by these authors, 1,199 (85.6%) were in the veins of the lower extremities. Of these, 502 were in the "short saphenous" (which we would interpret as intended to mean the deep veins in the calf), 160 were in the long saphenous, and some 537 in the iliofemoral veins. It is not possible to learn from the evidence given how many of the latter were extensions from the lower leg and how many were limited to the iliofemoral veins. In any case, since embolism from the long saphenous and from "primary" iliofemoral thrombophlebitis is rare,⁶ it is clear from these data, also, that the parent source of most emboli is at a site below the common femoral.

On the basis of the above considerations the deep veins of the lower leg must be regarded, by far, the most common site of origin of venous thrombosis. The condition is dangerous because the thrombus frequently extends proximally as a long, soft clot, which, if detached, produces a fatal or nonfatal embolus, depending upon its size.

To anticipate such an accident is obviously preferable to the heroic type of interference described by Nystrom.⁷ Intravenous heparin⁸ seems effective, but it is not likely to become a universally adaptable method (1) be-

cause of its expense, and (2) because it involves too much of a burden on the patient to justify its routine employment in postoperative patients, even if limited to people of middle and advanced age. Since the preventive measures now in general use⁹ are frequently unsuccessful, even when conscientiously applied, thrombosis continues to be an unsolved problem. In these circumstances, division of the femoral vein is the only promising alternative as an efficient prophylaxis against embolism. This procedure was first recommended and applied by Homans and has been so employed occasionally, by others^{10, 11, 12}. Our purpose is to show why its adoption as a routine measure is essential if a significant reduction in the morbidity and mortality from embolism is to be achieved.

As stated at the beginning of this communication, the procedure should be utilized when thrombosis of the deep veins of the lower leg is *present or suspected*. Such a diagnosis requires careful and repeated examination of the lower legs for the earliest manifestations of this disease. These are (1) pain or tenderness in the sole of the foot or ankle, but usually in the calf muscles, (2) pain on forced dorsiflexion of the foot (Homan's sign⁹), (3) slight fever, (4) increased local heat (delayed cooling—Pilscher¹³), (5) local edema, (6) induration, (7) fulness of superficial veins, and (8) slight cyanosis.^{*} Unfortunately any or all of these signs and symptoms may be absent.

In the total absence of local evidence of thrombosis, the diagnosis of course cannot be made unless a pulmonary embolus discloses its presence. Fatal embolism may occur as a first event in the total absence of localizing signs or symptoms. Such unanticipated catastrophes cannot be avoided when the site of thrombosis is in such inaccessible areas as the pelvic or iliac veins. But since the large majority, as already indicated, arise in the deep veins of the lower leg, many fail of anticipation not because the thrombosis is clinically undemonstrable, but because a meticulous inspection of the lower legs in immobilized individuals, postoperative and otherwise, has not yet become a clinical habit.

Bauer¹⁰ recently introduced a technic, similar to that described by Dougherty and Homans,¹⁸ which is apparently effective for the adequate visualization of the deep veins of the lower extremity. A venogram, taken after 20 cc. of a 35 per cent solution of perabrodil† are slowly injected

^{*} The term "phlebitis" as used in the subsequent text, refers to this clinical syndrome, which is different, at least in degree, if not in type, from the condition commonly known as milk-leg—a far more outspoken syndrome, in which the process apparently centers in the iliofemoral veins and is accompanied by considerable fever and marked edema of the whole leg, but which is only rarely responsible for pulmonary embolus. Incidentally, the prevailing opinion that so-called primary iliofemoral thrombophlebitis arises, *ab initio*, in the iliofemoral veins is based on the fact that the clinical signs and symptoms are first noticed in the region of these veins. The accumulating evidence from adequate pathologic studies raises the suspicion that the process in many, if not most, instances is an extension from a silent thrombosis lower down.

† Diodrast is probably the best approximation on the American market.

into the small saphenous vein, exposed under local anesthesia, at the ankle (with the heel elevated on a 6 cm block), will disclose the presence or absence of a deep phlebitis. The special virtue of this procedure is two-fold (1) If a nonfatal embolus has occurred in the absence of local signs or symptoms of phlebitis, the side on which it exists can be determined, (2) by disclosing the extent of involvement of the femoral vein, a guide to the level for effective prophylactic division of the great veins in the groin is provided. Venography, immediately following the rapid injection of 20 cc of a 50 per cent solution of perabrodil into the internal saphenous at the mid thigh, can be utilized to determine whether the process has progressed beyond this region.

A policy of routine division of the femoral vein, when thrombosis is discovered by local evidence or by the occurrence of a nonfatal embolus, can receive sympathetic consideration only if the risks of inaction can be shown to outweigh, by a good margin, the risks of intervention. The risks of inaction cannot be assessed with precision from existing statistical evidence because many cases of thrombosis and of embolism are frequently overlooked or wrongly diagnosed.¹⁴⁻¹⁷ However, an approximation to the facts is possible. Pilcher's¹³ data shows that about one person in 20, who had clinically recognizable thrombosis, died later of embolism, and about one person in 12 who had a previous nonfatal embolus, died of a subsequent embolus. The evidence from the recent studies of Barker, *et al*,⁴ is even more striking. One person in 17 (30 out of 502 cases of thrombophlebitis in the "short saphenous"), who had clinically recognizable thrombosis in the deep veins of the lower leg, died later of embolism, one person in five or six with a previous nonfatal embolus (124 out of 678 cases of nonfatal embolus) died of a subsequent embolus. Barker, *et al*, conclude that if all fatal embolisms which were preceded by a clinically diagnosed nonfatal embolism could be prevented, the total number of the fatal embolisms would be reduced by about one-third." In our view, the foregoing facts constitute a situation akin to any threatening emergency in which there is a substantial likelihood of a fatal complication.

To illustrate the disastrous consequence from failure to intervene when thrombosis in the deep veins of the lower leg is known to exist, we cite the following recent experiences.

Case 1—An obese, hypertensive diabetic female, age 63, entered the hospital with a painful left great toe which showed signs of vascular insufficiency. For two years she had had signs and symptoms of peripheral vascular disease of both legs, and for five weeks, pain in the left leg while resting. After conservative measures failed to afford relief amputation was advised, but the patient insisted on relief of pain by a less radical method. Three of the sensory nerves to the foot were crushed, through appropriate incisions in the lower third of the leg, on the twentieth day of her hospital stay. The following day she complained of an unusual amount of pain in the calf of this leg, examination of which showed edema, slight cyanosis and venous engorgement. The temperature was 101° F. Because of the prevailing lack of a decisive policy as to whether or not to divide the femoral vein in phlebitis of the leg, decision was deferred.

The next morning on getting into a chair she collapsed, became cyanotic and died suddenly with all the classic signs and symptoms of massive pulmonary embolus

Case 2—A male, age 43, was admitted for Buerger's disease of both lower extremities and hypertension. The deficiency in the circulation of the left leg was due more to vasospasm than to organic occlusion. Accordingly, a left lumbar sympathectomy was performed. Five days later there was slight hemoptysis, his temperature rose to 103° F, and he showed signs in the right lower lobe which were interpreted as due to an infarct, with superimposed pneumonitis. He was clinically cured of this complication by the twelfth postoperative day. But on the fifteenth postoperative day he complained of slight pain in both legs. There was tenderness on pressure over the calf muscles, and phlebitis was suspected. In this, as in the preceding instance, division of the femoral vein was under consideration but not carried out. Twenty-four hours later he was seized with substernal distress, became dyspneic and cyanotic, and died in less than ten minutes.

Case 3—A male, age 69, walked into the hospital complaining of pain in the right lower quadrant of the abdomen of 36 hours' duration. There was vomiting at the onset of the illness, and he had had two severe chills on the day before entry. Until then he had always enjoyed good health. Physical examination showed a temperature of 104.5° F, pulse 90, respiration 20. The cardiorespiratory system was within normal limits. Except for a right hydrocele there was nothing else of note except evidence of a mass in the right lower quadrant which was presumably an appendiceal abscess. Under local infiltration anesthesia, an acutely inflamed appendix was removed. There was a large mass of inflamed mesentery around the appendix and evidence of local pyelphlebitis. The following day the temperature was normal and remained so. Because of his age and his apparent state of well-being, he was allowed out of bed. He sat up most of the day and walked during the last two of the subsequent six days, during which he felt entirely well. On the afternoon of the sixth postoperative day he complained for the first time of pain in the right calf. Examination showed moderate edema of the calf and ankle and tenderness on deep pressure over the calf muscles. He was put to bed with the intention of dividing the femoral vein the following morning, should no improvement in the phlebitis occur overnight. At 7 A.M. of the seventh day, after an entirely comfortable night, while talking to the nurse, he suddenly felt acute substernal distress, became dyspneic and pale, and died within a few minutes.

COMMENT—In all three patients the existence of phlebitis in the lower leg was known in advance of the detachment of the embolus. The evidence for phlebitis was clear-cut in Cases 1 and 3, and suggestive in Case 2. A complacent attitude toward the phlebitis in the latter instance could hardly have been justified on the basis that the signs and symptoms were not outspoken. The first embolus was sufficient notice of its presence. The experience in all three patients demonstrates the fact that there is no period of watchful-waiting that may be considered a safe interval between the onset of phlebitis and the liberation of an embolus. Had a policy of intervention, by division of the femoral vein, instead of one of hesitation been adopted, there is good reason to believe that death could have been prevented.

The prophylactic effectiveness of division of the femoral vein cannot be proved in any given case in which it is undertaken, for no one can assume that, otherwise, an embolus would have been discharged from the area caudad to the division. Its value can be affirmed with certainty only after routine division in a very large series of patients with phlebitis should

succeed in demonstrating an incontrovertibly lowered incidence of pulmonary embolus, fatal or nonfatal. Nevertheless, the protective effect of dividing the femoral vein seems to have been demonstrated in the following illustrative cases.

Case 4—A male, age 40, with well-marked thromboangitis obliterans of the left leg, was submitted to denervation of the foot for relief of pain, by crushing the appropriate sensory nerves above the ankle, under spinal anesthesia. Five days later he complained of pain in the left calf. Fever, leukocytosis and edema of the leg were noted at the same time. That evening he complained of pain in the left anterior chest, aggravated by inspiration. On the sixth day there were dyspnea, cyanosis and signs of consolidation in the left lower lobe. The roentgenologist interpreted the film of the chest as showing "consolidation at the left base, probably a pneumonitis, possibly an infarct." On the seventh day the left femoral vein just below the profunda was divided. Hippuran was injected into the distal end of the vein, and the roentgenogram showed a cone-shaped filling defect. Slow resolution of the pulmonary process occurred and he seemed much improved on the sixteenth day. But on the eighteenth day he complained of pain in the right calf which was tender on pressure and there was slight pretibial edema. Fever recurred, and on the twenty-fourth day there was evidence of infarction in the right lower lobe. The right femoral vein was divided just below the profunda that evening. Two days later he complained of pain along the right femoral vein in Hunter's canal. Resolution of the phlebitis and the pulmonary infarction occurred, and he was discharged, well, 12 days after the second vein was divided.

Case 5—A female, age 47, had a cholecystectomy, under nupercaine spinal anesthesia. Nine days later she felt some pain in the right calf but did not mention it to the house officer. On the eleventh postoperative day she was allowed to sit up with the feet over the bedside. That afternoon she was dyspneic and felt "a heaviness over the breast bone, like a cold coming on." The temperature rose, the pulse increased to 130, and respirations to 30, but all of these signs and symptoms subsided the following morning. That afternoon she went into collapse, the blood pressure fell to 45/30, there was dyspnea, cyanosis, sphincter incontinence, cold, clammy extremities, and a rapid thready pulse. The next morning there was tenderness in the right calf and the patient then admitted pain in this region during the preceding four days. A roentgenogram showed an infarct in the right lower lobe. Under local anesthesia, the right femoral vein was divided. After division the distal segment collapsed, suggesting a block to the flow distally. She was discharged, cured, 12 days later.

Case 6—A female, age 54, complained of sudden pain in the right chest on the third day following the repair of a large incisional hernia. Fever, tachypnea, and signs of consolidation in the right upper lobe were noted the next day. A roentgenogram showed an area of increased density in the right upper lobe, which was interpreted as atelectasis by the radiologist. The right leg was swollen, and there was some pain deep in the adductor muscles of the thigh. Two days later the right femoral vein was divided. Roentgenography of the vein, after hippuran had been injected distally, showed a definite mottled filling defect, consistent with a large thrombus at the midportion of the vein, about 7 cm long. The signs in the lung persisted for another week and then disappeared.

Case 7—A male, age 65, with a carcinoma of the rectosigmoid, showed signs of pneumonitis at the right base 16 days following a cecostomy for acute obstruction of the colon. A roentgenogram was interpreted as showing "atelectasis, or perhaps an infarct." There was pain in the right chest but no evidence of phlebitis in either leg. Two days later the left leg was slightly swollen at the knee, but there was still no other evidence of phlebitis in either leg. Four days later there was much bloody sputum. Both legs were now swollen. Eleven days later pain in the right chest recurred, and there was marked hemoptysis. After a three-day interval, free from symptoms, he complained of

pain in the left calf. The same day both femoral veins were divided, with subsequent rapid disappearance of all signs and symptoms in the chest.

COMMENT—In this patient an infarct was the first evidence of phlebitis. The appearance of bilateral swelling, along with further embolism, and finally pain in the left calf, led to bilateral division of the femoral veins with the desired result and without untoward sequelae. Intervention following the occurrence of the first infarct would have necessitated bilateral ligation and division because of the total absence of localizing evidence of phlebitis. Division of the femoral vein on an obviously involved side, as a matter of fact, will not guarantee protection against further embolism, for there may be a silent phlebitis on the opposite side. In this connection the frequency with which Neuman² found bilateral thrombosis (52%) by anatomic dissection must be borne in mind. Since the radiologic diagnosis of phlebitis, not otherwise recognizable, is now possible,¹⁰ hesitation to intervene when a nonfatal embolus has occurred can no longer be justified on the ground that a guide to the site of the phlebitis is lacking. In the present controversial phase of the problem, however, one may be content with unilateral ligation if there is an obviously involved side.

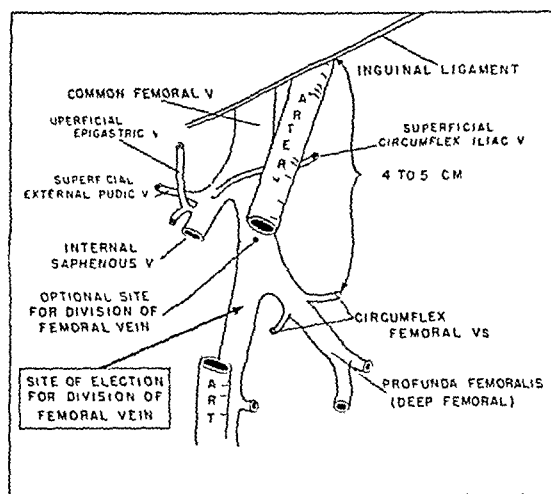


FIG 1—The anatomy of the region involved in division of the femoral vein.

Division of the femoral vein just below the vena profunda is the most desirable site for blocking the discharge of an embolus from the deep veins of the lower leg, because no proximal segment of vein with a sluggish stream is left, while the profunda and the internal saphenous remain as adequate pathways for the return flow of blood. The operative exposure necessary for this purpose (Fig 1) permits a simultaneous examination of the vena profunda and a division of this tributary if it contains a thrombus or clot or if there is preoperative evidence of thrombosis in the deep tissues of the thigh (18 per cent in Frykholm's series). If division of the common femoral is necessary in order to shut off the profunda as well as the femoral, it may be done. A slight amount of transitory edema due to the division itself may result. Division of the femoral vein does not affect the phlebotic process adversely, on the contrary, the signs and symptoms generally subside rather more promptly than otherwise. This is evidently due to the fact that division of the vein simultaneously divides some of the sympathetic pathways involved in the reflex vasospasm, which not infrequently adds to the pain and edema attributable to the phlebitis.

If there has been much delay in the division of the femoral vein and

the soft clot has advanced beyond the common femoral, it can be sucked out. One may, however, find instead a firmly fixed thrombus, as in the following cases

Case 8—A male, age 70, was allowed to sit up on the ninth day following the repair of an incarcerated inguinal hernia. The next day he complained of pain in the right calf. There was deep tenderness over the calf and pain on passive dorsiflexion of the foot, but no swelling or fever. Division of the femoral vein was advised but refused. Three days later fever occurred, but the calf pain and tenderness had disappeared, while tenderness appeared in the femoral triangle. Division was again advised and this time accepted. The vein was found thrombosed and surrounded by an organizing exudate. A section of the vein was removed and showed beginning organization of a thrombus. Forty-eight hours later the temperature was normal, and the patient was discharged 96 hours after division.

Case 9—A male, age 48, complained of pain in the right lower leg on the fifth day following a laminectomy for the removal of a ruptured intervertebral disk. Examination of the leg showed mottled cyanosis of the ankle and edema and tenderness over the calf muscles. Early on the sixth postoperative day he suddenly went into collapse, became cyanotic and complained of pain in the lower left chest which was aggravated by inspiration. An electrocardiogram showed no changes suggestive of coronary occlusion. A roentgenogram on the seventh postoperative day was interpreted as showing an infarct at the left base. There was gradual improvement in the phlebitis and the pulmonary complication until the sixteenth postoperative day when he developed dyspnea and severe pleurodynia in the right axilla. A roentgenogram showed right pleural effusion and a probable underlying infarct. At this time edema of the right thigh was observed. The right femoral vein was then divided, but thrombosis extending above the inguinal ligament was noted. An excised segment of vein showed an organizing thrombus with perivascular edema and inflammation. Edema of the right ankle persisted for a month thereafter, and toward the end of this period edema of the left ankle was present.

COMMENT—It is difficult to be certain that the right femoral vein was the source of both emboli. That it may possibly have been the left is suggested by the appearance of edema in the left leg at a late stage in the convalescence. There was an interval of 17 days between the onset of phlebitis in the right calf and the division of the right femoral vein. During the interval two successive infarctions occurred. The advancing thrombosis had by this time extended beyond the site of election for dividing the vein. This case illustrates the fact that the thrombosis does not always remain a localized process, with a superimposed soft clot. Waiting may allow the thrombotic process to advance beyond the point where division at the level herein recommended can be useful.

The indications for division in these circumstances have not as yet been clearly defined.¹⁵ It is generally true that if the process extends proximally as a fixed thrombus, instead of as a clot, the danger of embolus is distinctly lessened. However, occasionally embolization will occur. This is well illustrated in the following case, although the thrombus in this instance involved the long saphenous rather than the deep femoral.

Case 10—A female, age 69, entered the hospital, with acute intestinal obstruction. At the same time acute thrombophlebitis involving the entire right varicose saphenous vein was noted. A Miller-Abbott tube achieved satisfactory deflation of the intestine.

within 48 hours. After four more days of restorative therapy, during which the right leg had been kept elevated, without significant change in the thrombophlebitis, she was prepared for exploration for carcinoma of the colon. While in position for nupercaine spinal anesthesia, with the legs firmly flexed on the abdomen, her respirations became rapid and shallow and the blood pressure fell to 60 systolic after 10 cc of 1,500 nupercaine had been injected. Two doses of intravenous neosynephrin were given, the anesthetist expecting that she would shortly respond to the vasopressor treatment. Death followed shortly thereafter, and was attributed to nupercaine poisoning. Autopsy revealed an obstructing carcinoma of the cecum, with hepatic metastases, and a large, fresh embolus plugging the pulmonary conus. The embolus was shown to have arisen from the thrombus in the saphenous vein from which it broke off probably during the spinal anesthesia.

COMMENT—The danger of a pulmonary embolus from saphenous thrombophlebitis is regarded as inconsequential. If manipulations of a patient can detach a presumably firmly fixed thrombus, the relative ease with which a patient's own movements or the manipulations of an attendant can dislodge a soft propagating clot in the deep system is obvious.

Division of the popliteal instead of the femoral vein is not satisfactory, as the following experiences show.

Case 11—A female, age 70, complained of severe constant pain in the right calf and ankle 12 days after a left radical mastectomy for carcinoma of the breast. Marked edema, venous engorgement, slight cyanosis along the lower half of the right tibia and exquisite tenderness on pressure over the right calf were noted. Ligation (without division) of the right popliteal vein was performed immediately. No clot or thrombus was observed in this vessel. Ten days later there were signs and symptoms of a pulmonary infarct in the right lower lobe, confirmed by a roentgenogram of the chest. At the same time tenderness appeared along Hunter's canal, suggesting a new thrombus proximal to the site of ligation. Division of the femoral vein was advised but refused. The intensity of pain in the lower leg was much greater after than before ligation of the popliteal vein. The pain, edema and cyanosis were increased by the ligation, perhaps because the obstruction to venous return was too extensive. Mild edema of the leg was still present eight weeks later.

Case 12—A male, age 52, 12 days after the repair of a recurrent left indirect inguinal hernia, experienced pain in the right calf muscles especially on dorsiflexion of the foot. There was no edema or cyanosis. Two days later the popliteal vein was divided. Following division the pain increased in intensity, fever occurred and edema appeared. The pain subsided somewhat after ten days, but he was not entirely free of pain three months after discharge from the hospital. Six months later he still had edema.

COMMENT—Division of the popliteal vein should be avoided not only because it seems to aggravate the symptoms and prolong the morbidity, but also for the following reasons: (1) The thrombus or clot in the deep veins may be found extending beyond the popliteal. (2) Since the femoral vein below the profunda receives few branches of any consequence, division of the popliteal results in a sluggish column of blood which may permit the formation of a clot of sufficient length, if detached, to plug a large branch of the pulmonary artery.

A consideration of the risks involved in division of the femoral vein must take account of the possibility of initiating a thrombosis proximal to the site

of division. Since division just below or above the profunda does not leave a long proximal segment of vein lacking large active tributaries, there is no good reason to fear this possibility. In any case, there is no evidence of its occurrence in our experience, and no mention of it is made in the experience of Homans,¹⁵ Faxon,¹⁶ and O'Neil¹⁶ when the vein at the site of division was free of clot or thrombus.

The risks involved must also take account of the possible undesirable late sequelae of the procedure, namely persistent edema, pain or functional disability. Such sequelae do not justify the conclusion that the division *per se* is any more responsible for them than the phlebitis for which the division was done. We cannot find, in our experience, that division below or above the profunda contributes, in any substantial degree, to what might have been expected had nothing been done. Indeed, as Homans⁹ and Bauer¹⁰ have repeatedly observed, the process was commonly observed to subside more quickly than otherwise as a direct consequence of the operation.

In a follow-up study, two to 20 months after discharge from the hospital, all patients with phlebitis, whether the femoral vein was divided or not, showed varying degrees of edema of the leg. In a few instances the edema was so slight that a woven bandage was not required. In the majority, the swelling, though moderate, could be controlled easily with appropriate support, without support the swelling at the end of the day caused heaviness and discomfort. Swelling was most marked in two patients in whom femoral vein exploration revealed extension of an organized thrombus beyond that level. Apparently the higher the obstructing thrombophlebitis, the greater the swelling when the patient becomes ambulatory, regardless of whether or not the vein has been ligated.

In several patients who were ambulatory before the diagnosis of thrombosis was made, no increase in swelling was observed after the femoral vein was divided. None of those who were operated upon developed, during the follow-up period, a degree of edema even remotely resembling that seen in "milk-leg." None gave evidence of postphlebotic induration or ulceration.

Efforts to locate the thrombus by roentgenographic visualization of the veins distal to the point of division during operation have yielded only occasional positive results. There were two patients in whom a filling defect indicative of a clot or thrombus was clearly demonstrated. In others the retrograde current of radiopaque medium was abruptly halted by valves or obscured by excessive dilution. This is to be expected in most instances because the radiopaque medium is injected usually at a considerable distance from the thrombus. Preoperative venography by the technic of Bauer¹⁰ promises to render other methods obsolete.¹⁹

Since Hampton and Castleman,¹⁴ Neuman,² and others¹⁷ have demonstrated in autopsy material a high incidence of pulmonary emboli in non-surgical patients (without cardiac disease), the problem of pulmonary embolism from deep phlebitis can no longer remain the exclusive concern of the surgeon. The tendency to the development of venous thrombosis, a

necessary precursor of embolism, must be regarded as common to adults, especially over the age of forty, confined to bed, whether at home or in a hospital

SUMMARY AND CONCLUSIONS

Thrombosis of the deep veins of the lower leg is the focus of origin of the great majority of pulmonary emboli

Pulmonary embolism until recently has been regarded as a dramatic post-operative catastrophe for which adequate prophylactic or therapeutic measures are not available. This is no longer tenable except in the case of massive embolus which has occurred in the absence of detectable signs of venous thrombosis of the lower leg and in the absence of a previous episode of embolism

If the surgeon will conscientiously observe the patient from the very beginning and throughout the postoperative period for the signs and symptoms of phlebitis in the deep veins of the lower leg, he is likely to discover the existence of at least suspicious evidence of phlebitis in a much larger number of instances than heretofore in advance of the discharge of an embolus

If the evidence of phlebitis in the lower leg is clear-cut, immediate division of the femoral vein below or above the profunda should be done (bilaterally if both legs are involved). If embolism has not yet occurred, the procedure may be considered a justifiable prophylactic measure. If an embolus has been discharged, however massive it may be, so long as it is not fatal, immediate division of the femoral vein is the one most effective measure remaining to prevent the discharge from its commonest source of still another embolus which may prove fatal

If the evidence of phlebitis is only presumptive, a decision can be reached by the venographic technic of Bauer

If embolism has occurred in the total absence of signs or symptoms of phlebitis, the process will usually be demonstrated and lateralized by the venographic technic of Bauer. An embolus henceforth can be assumed to have arisen from the pelvic or other inaccessible veins only when no involvement of the deep veins of either lower extremity is shown to exist by employment of this technic

There is no good evidence that division of the femoral vein involves any significant immediate risk or adds to the disability created by the phlebitis itself. On the contrary, aside from its prophylactic value for embolism, division appears to exert a favorable influence on the course of the disease probably because of the concomitant disruption of some of the pathways involved in the accompanying vasospastic reflexes

Because pulmonary infarcts and fatal pulmonary embolism due to phlebitis of the lower leg occur frequently in nonsurgical as well as surgical patients, the therapeutic problems involved become the common concern of the internist as well as the surgeon

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THE MANAGEMENT OF LYMPH NODES IN THE NECK— METASTATIC FROM CARCINOMA OF THE MOUTH*

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It is generally conceded that cancer is a local lesion at first, that there is no means of determining how soon metastasis may take place, or whether it has taken place, until considerable progress in the secondary growth has occurred, that removal of the local lesion only is useless if metastasis, whether recognizable or not, has taken place. Nevertheless a large volume of literature exists arguing against the value of lymph node excisions in intra-oral cancer.

The local lesion in buccal carcinoma is rarely the cause of death. Metastatic involvement of the cervical nodes, with its sequelae, is the usual cause. Treatment of the cervical drainage area may be by disregard, by radiation, by surgery, or by a combination of the latter two. A defeatist attitude toward the ultimate result of any type of treatment of any carcinoma is still all too common among the lay public, the general medical profession, the general surgeon, and the general radiologist. This is one of the reasons why treatment, recommended by surgeons or radiologists specializing in the cancer field, is often carried out in an indifferent fashion by others. The motions of giving treatment are gone through, but, evidently with no expectation of permanent good result. The mortality from buccal carcinoma is shown in Table I.

TABLE I
CANCER OF THE BUCCAL REGION (NOT INCLUDING PHARYNX)
IN UNITED STATES REGISTRATION AREA

	Deaths		Per 100 000	
	1914	1935	1914	1935
Cancer of				
Lip	376	727	0.6	0.6
Tongue	614	1,076	0.9	0.8
Mouth	230	550	0.3	0.4
Jaw	851	999	1.3	0.8
Others	199	600	0.3	0.5
Totals	2,270	3,952	3.4	3.1

Since 1914, the advent of external radiation and interstitial radium has added a powerful weapon to cancer treatment in many locations. In the early years its use was in the experimental stage and statistics could not be considered of permanent value. For several years past many of its advocates have been sufficiently satisfied with their results to advise against the use of surgery.

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in some locations. One of these is the routine dissection of lymph nodes in the neck—metastatic from carcinoma of the mouth.

Block dissections of the neck were never a popular operation with the general surgeon. It is a field in which he is not called on to work frequently. The procedure is a prolonged one requiring patience, meticulousness, and an enthusiasm about the ultimate result. An intimate knowledge of the anatomy of the neck is required. For these various reasons, block dissections of the neck have been in many instances a name only, rather than a true description of the method which was carried out. Therefore, the general surgeon was often pleased to side-step these procedures, when he found that a radiotherapist would take them off his hands.

Here is one of the most obvious lesions, causing early symptoms, not requiring any complicated aids to diagnosis, which should have been affected by lay education at least as much as any other lesion. The local lesion can be eradicated by either radiation or surgery, and this must always be done before operation on the lymphatic drainage area which is affected. I believe the local treatment usually has been rendered well for some years past. But it is the metastatic involvement which generally kills. Block dissections of the neck seem to be performed less frequently and, in spite of radiotherapy, the death rate has improved but little over a period of 21 years. It can be arranged from this that the lymph node problem is not being handled vigorously enough.

Except in the radio-sensitive Grade III and IV lesions, there is little definite evidence that external radiation has a permanent arresting effect on squamous carcinoma—metastatic to the cervical nodes. Neck surgery should not be undertaken in Grade III and IV lesions or in lymph-epithelioma. Complete regression of epidermoid carcinoma, metastatic in cervical nodes, from external radiation alone has been reported by some authors. Since an inflammatory node can be mistaken readily for a metastatic node, these results must always remain inconclusive. Many of the most experienced radiologists do not agree that this complete regression occurs. Possibly by most radical irradiation this could be obtained, but I have not known of this being administered except in advanced metastases. Most radiologists claim few, if any, five-year arrests with pathologically proven involved nodes.

It is commonly argued that prophylactic neck dissections, *à la*, when lymph nodes are not palpable or, being palpable, are believed not to be involved, is unnecessary surgery, since often the pathologist fails to find any involvement. This does not necessarily mean that no metastasis to the region excised has occurred. The pathologist has not *found* carcinoma in any of the sections which he examined. Naturally, he does not make serial sections of all the tissue sent to him, but of nodes or regions which appear suspicious to him. It is possible, theoretically at least, for one or a few metastatic cells to be present in a regional lymph node and impracticable for the pathologist to find them. Without a prophylactic neck dissection such deposits may continue to grow.

In a series of 64 patients with carcinoma of the lower lip, in whom no lymph nodes were felt and in whom prophylactic neck dissections were performed, we¹ found metastases in nine instances, or 14 per cent. Simmons and Daland² reported similar findings in 25 per cent. Morrow,³ of our institution, found that of 18 tongue cases, in which it was stated that no nodes were palpable and prophylactic neck dissections were performed, metastases were present in seven instances, or 39 per cent. Phillips,⁴ in 31 cases of buccal carcinoma with no clinical metastases, found microscopic involvement in 16, or 51.6 per cent. Simmons,⁵ in 20 cases of oral carcinoma with non-palpable nodes, found seven which proved to be cancerous, or 34 per cent. We do not grant that lack of palpable nodes in the neck means that metastasis has not occurred.

Among 98 patients in our series¹ with carcinoma of the lower lip in whom lymph nodes were felt and neck dissections were performed, tissue examination proved that metastases were present in 32 instances, or 33 per cent, and the remaining cases showed hyperplasia only. Regaud⁶ states that palpable nodes are cancerous in 60 per cent of these cases. Morrow³ found microscopic involvement in 25 of 48 tongue cases with palpable nodes, or 52 per cent. Phillips,⁴ in 59 cases of buccal carcinoma with clinical metastases, found microscopic involvement in 37, or 63 per cent. Simmons,⁵ in 22 cases of oral cancer with palpable nodes, found 12 involved, or 55 per cent. We do not grant that a man experienced in this field can decide whether enlarged nodes are involved or not, as long as there has been no break through the capsule. Therefore, we are unable to agree that without neck dissection frequent follow-up examinations offer assurance to the patient as to the time when operative intervention is indicated. All agree that once a node has become fixed the likelihood of arrest of the disease by any method is slight.

There is an interval in all these cases before metastasis occurs. Adequate local treatment will result in 100 per cent arrest at that time. Unfortunately, we have no means at present of knowing in any individual patient that metastasis has not occurred. Except in certain lip lesions, we believe that buccal cancers require some type of removal of regional nodes, on account of the danger of metastasis having occurred already.

The percentage of patients who have metastases varies with lesions in different portions of the oral cavity. It is difficult to obtain statistics on how many out of each 100 persons with these different lesions will develop metastases. It seems conservative to expect 20-25 per cent in lip cases (24 per cent found in my series), 45-50 per cent in tongue cases (47 per cent found in Morrow's³ series), and 50 per cent in cheek cases (51 per cent during observation in Martin's⁷ series). I believe that nearly all of these are doomed to death if the metastases are treated by external radiation therapy only.

The direction of metastatic spread is more definite and localized from these lesions than from most cancers in other locations. The different regional

nodes seem to act for a longer time as a bar to further spread of metastases. Technically, complete excision of the region of node involvement can be undertaken with more assurance than in most other regions. Except when involvement is found in the supraclavicular region, it is possible to excise the group of regional nodes next beyond the point where any involvement is found. This should always be our aim.

We make a practice of marking excised neck specimens so that the pathologist can tell exactly what regions are found involved. In cancer of the lower lip our custom up to a few years ago was to perform a block dissection of the neck as far down as the omohyoid-crossing of the jugular vein. This dissection was bilateral, at two operations, if the lesion involved the middle third of the lip. In 46 specimens showing metastatic involvement of the nodes, this was limited to the submaxillary or submental regions in 40 instances. In the remaining six, all showed evident clinical involvement with carcinoma in the neck before operation. Carcinoma was never found in nodes other than the submaxillary or submental when lymph nodes were not palpable in these regions before operation. Figi⁸ states "Extension of the malignant process through the lymph vessels draining directly into the deep cervical nodes or those entering the mental foramen rarely occurs, so that removal of the cervical nodes along with the submental and submaxillary groups is scarcely justifiable as a routine procedure." We agree with this statement.

In 1933, we¹ presented a group of 193 patients who had had neck dissections for carcinoma of the lower lip, with a mortality of 11.4 per cent. We find that this publication has been used as an argument against neck dissections. Later we analyzed this operative mortality further. We found that the majority of deaths occurred when some more extensive procedure than merely a neck dissection was carried out, *e g*, a bilateral block dissection at one operation, an extensive plastic procedure on the lip, or a partial resection of the jaw. Among 163 patients who had block dissections to the omohyoid-crossing, with no more extensive procedure on the lip at the same time than a V-excision, there were nine deaths, or 5.5 per cent. Since bilateral block dissections were effected on many patients at two operations, these 163 patients had 214 block dissections. One might, therefore, consider the mortality expected from this operation as 4.2 per cent. This included operations for all stages of lymph node involvement and was not limited to prophylactic neck dissections. If limited to the latter, the mortality would have been still lower. We might say, then, that of an expected mortality of 20 per cent from development of metastatic lymph nodes we were salvaging 15 per cent immediately after block excision to the omohyoid-crossing. We believed that this was sufficient to justify the operation, but it was still large enough to be a real argument against prophylactic neck dissection.

Therefore, as a result of our analysis of the lymph nodes found involved, we changed to a suprahyoid dissection only in those patients in whom we thought there was no evidence of metastases. This has now been effected in 81 patients with one death, or 1.24 per cent. This occurred on the fifth day

postoperative from pneumonia, in a man, age 73. It was thought by three examiners, preoperatively, that a submental node was probably involved. No metastasis was found. The anesthetic was rectal ether.

Involved nodes were found 14 times, or 17.3 per cent. However, this operation was performed in some instances where, on account of age or general condition, it was thought that, even though nodes might be involved, a more extensive neck dissection was inadvisable. This percentage, therefore, does not represent our findings of involved nodes in prophylactic neck dissections. When involved nodes are found in the submaxillary or submental regions, we believe a further block dissection should be performed to the omohyoid-crossing as prophylaxis.

Figi's⁸ mortality for the suprahyoid operation in 549 patients was 0.18 per cent. We believe the mortality for this operation should not be more than approximately 1 per cent. This would represent an immediate postoperative saving of 19 of the 20 per cent loss expected from cervical metastases. This low mortality effectively answers one of the arguments against prophylactic neck dissection.

What is the expected arrest when proved involved nodes are found? Since June, 1924, among the neck dissections which have been performed in carcinoma of the lower lip, metastatic involvement has been proved in 54 patients. It is fair to state that in the earlier years patients were operated upon with fixed nodes or jaw attachment, in whom an operation would now be considered contraindicated. Some of these patients were dead within a brief period, when it had been recognized at operation that the metastatic lesion, even grossly, had not been entirely removed. These factors must be taken into account in evaluating our results following neck dissection. These are shown in Table II.

TABLE II
RESULTS IN LIP CASES WITH INVOLVED NODES

	No. of Cases
Died in hospital	8
Died within one year of metastases	6
Died within one year cause unknown	1
Died within two years of metastases	6
Died within three years of metastases	1
Died within four years of metastases	1
Died of other causes after being free of disease over five years	3
Followed for less than one year or lost immediately	9
Known to be well 12-18 months	2
Known to be well 18-24 months	2
Known to be well 2-3 years	1
Known to be well 3-4 years	1
Known to be well 4-5 years	2
Known to be well over 5 years	7
Known to be well over 10 years	4
Total	54

Out of 54 patients with carcinoma of the lower lip with proved metastatic involvement in the nodes of the neck, 14 had their disease clinically arrested

over five years, or 26 per cent. Twenty-three are known to be dead, either while still in the hospital or later of metastases, or 43 per cent. The remainder have not been followed for a five-year period, and many of these we have been unable to find. At least 26 per cent were arrested for five years, all of whom we believe would have been dead except for this treatment. Figi's⁸ figure for five-year arrest, when lymph node involvement is found, is 39 per cent.

With operative mortality not over approximately 1 per cent for suprahyoid neck dissections, with a five-year arrest of 26-39 per cent, when nodes are found involved, we believe it is unjustifiable not to excise the regional lymph nodes, usually, in carcinoma of the lower lip. With the above considerations in mind, a routine for lower lip cases has been used in the Cancer Unit of the New York Post-Graduate Hospital for over five years.⁹

Metastases from carcinoma of the lip have been my assignment at our clinic. Other men have worked on metastases from other sources about the mouth. Morrow³ has published his findings concerning the tongue. The metastatic spread is entirely different. With a unilateral lesion the first evident node involvement may be on the opposite side of the neck or in either supraclavicular region. I lost one patient one and one-half years after operation from a supraclavicular involvement on the opposite side. In addition to the local removal, I had performed a block dissection on the same side to the clavicle and on the opposite side to the omohyoid-crossing. Metastatic nodes had not been found in either of these neck specimens, and there was never any evidence of local recurrence. Yet, about 15 months after his original operations, a swelling developed in the opposite supraclavicular region and he declined to report for observation until it had already become fixed. We agree with Morrow that, where the condition of the patient will permit, there should be complete removal of the lymph nodes to the clavicle from both sides of the neck. The five-year survivals with this operation were 50 per cent, as compared with 30.5 per cent for bilateral operations to the omohyoid-crossing and 14.8 per cent for unilateral operations to the omohyoid-crossing. The postoperative death rate from 1931-1935, inclusive, was 16.7 per cent. It was lowered from a previous much higher rate by undertaking more stages for completing the operative procedure. We might say, then, that, of an expected mortality of 45 per cent from metastatic lymph nodes, we were salvaging 28.3 per cent immediately after block excision of the regional nodes. Where nodes were proved involved at operation, the five-year survival rate was 11.5 per cent. Without node involvement, there were 32.4 per cent known five-year survivals.

For years I believed that cancer of the hard palate was not particularly likely to metastasize. However, in a small series MacFee and Zimany,¹⁰ of our clinic, found cervical metastases in 50 per cent. Probably a block dissection to the omohyoid-crossing on the side of the lesion is what is required here as prophylaxis.

In cheek cancer our series is too small to draw definite conclusions. Prob-

ably a unilateral suprahyoid block dissection is all that is required without clinically involved nodes, except when the lesion approaches the tonsillar region. Then a dissection to the omohyoid-crossing should be undertaken. Of course, in each of these instances if involved nodes are found, further dissection is carried out to the next lymphatic block.

CONCLUSIONS

Radiation therapy has apparently improved but little the results in metastatic involvement of the cervical lymph nodes. Much of the surgery of this region is inadequately performed to rid the tissue of cancer cells. The plan of approach to excision of nodes needs to be varied with the location of the lesions about the mouth. The mortality from block dissections can be brought to a point where prophylactic neck dissections show a real salvage value. Five-year arrests in intra-oral cancer will show little improvement with present known methods of care until the defeatist attitude toward treatment of metastatic nodes is overcome.

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TUMORS OF THE CAROTID BODY

CLINICAL AND PATHOLOGIC CONSIDERATIONS OF TWENTY TUMORS
AFFECTING NINETEEN PATIENTS (ONE BILATERAL)

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THE CAROTID BODY was first mentioned by von Halle²¹ in 1743, and was first described in detail by Luschka,¹¹ in 1862. It is a paired organ situated at or near the bifurcation of each common carotid artery. It is supposed to attain its full development when the individual reaches the age of about 20 years, but either it does not develop in many individuals, or, if it does, it is so small that it cannot be found even at necropsy. It is normally about the size of a grain of rice and is pinkish-gray or purple. It is supplied with blood from the carotid artery and its nerve supply is derived from the glossopharyngeal nerve, the sympathetic cervical ganglion and, sometimes, from the vagus nerve.

Considerable interest has centered in tumors of the carotid body, since the original communication of Marchand,¹³ in 1891. The literature^{1 2 5, 12 16 18} mostly contains reports of single cases or small groups of cases, and during the last 40 years, much has been learned of the life history of these unusual neoplasms. No surgeon, apparently, has had personal experience with more than a dozen cases of the condition, and for this and other reasons it was thought advisable to review data concerning a group of 20 such tumors for which 19 patients consulted the Mayo Clinic. Twelve of the cases included in this review have been reported previously (1931) by Rankin and Wellbrock.¹⁷ The series reported on by Rankin and Wellbrock included one case in which the tumor was bilateral, thus, although they reported on 12 patients, actually, their series described 13 tumors. Their case of bilateral tumor of the carotid body is included in our series, by extension, it is seen that we report on 19 patients and 20 tumors.

General Consideration—*Embryologically*, the carotid body is a complex structure developed in connection with the third mesodermal arch. Early investigators believed the carotid body to be vascular in derivation. However, the observation of Stilling,¹⁹ and others, that the organ contained chromaffin-positive cells has lent considerable support to the theory of origin of the carotid body in the sympathetic nervous system. At present the field is divided, but most observers concur in the belief of Kohn^{8 9} that the carotid body is homologous to the medullary portion of the suprarenal gland.

Anatomically, variations in size and position of the carotid body have been noted. Gomez⁶ measured 26 carotid bodies and found that the average diameter was 3.5 Mm for his series with extremes of .8 and 0.5 Mm. In another series, Bevan and McCarthy³ observed an inconstant relationship of the body to the bifurcation of the common carotid artery, but in nearly all cases the body was encapsulated and adherent to the larger arteries in the neck. In some cases the body was bilateral, in others it was unilateral. Atrophy and fibrosis were observed in the carotid bodies of elderly individuals.

Histologically, the chief cells observed resemble epithelial cells in being large, polygonal, and pale-staining. The cytoplasm is large in amount and is finely granular—these granules being chrome-positive in fresh tissue. Nuclei are eccentric, hyperchromatic, and frequently are vacuolated. A rich capillary network is observed and solid strands of endothelial cells are encountered. Ganglion cells, plasma cells and eosinophils have been described. All these cellular elements are grouped in the form of islands which are separated by fibrous septums springing from the capsule.

Physiologically, there is little or no evidence in favor of inclusion of the carotid body among the glands of internal secretion. The facts that it is frequently absent and that bilateral extirpation can be performed without the subsequent occurrence of untoward symptoms suggest that its function, whatever it may be, is negligible.

Tumors constitute the only pathologic lesion of the carotid body, and more than 200 cases of tumor have been recorded. It is not our purpose to review the literature on this subject because we believe that the material to be presented is fairly representative. We do wish, however, to enumerate, briefly, certain recent observations that have perhaps justified the inclusion of the anatomic and embryologic data previously detailed.

(1) In the presence of tumors of the carotid body the architecture of the normal body, in the matter of encapsulation and lobulation, is fairly well maintained.

(2) As in the normal body, polygonal cells and endothelial cells are present in varying numbers in the body affected by tumor—polygonal cells nearly always predominate.

(3) As in the normal body, the polygonal cells in the body affected by tumor have finely granular cytoplasm which has an affinity for chrome salts (for this reason fresh tissues always should be fixed in Zenker's fixing solution).

(4) Since these polygonal cells are probably epithelial in origin (sympathogonial derivatives), the tumors derived therefrom probably should be regarded as being chromaffinomata.

MATERIAL—Pathologic Aspects The pathologic material for this study consisted of 20 tumors of the carotid body removed surgically from 19 patients. The tumors were carefully studied grossly, and the interesting specimens were photographed. Careful measurement was made of each specimen, and notes were made on the relationship of the tumor to the carotid vessels.

in instances in which resection of the latter was necessary. Multiple blocks were then obtained and placed in fresh 10 per cent solution of formalin. From these blocks, sections were cut and stained routinely with hematoxylin and eosin. In all, some 75 microscopic sections were made available for study.

No attempt is to be made herein to review the pathologic criteria that have been established for tumors of the carotid body. The observations of others were confirmed in the present series, and the important features are outlined in the following paragraphs.

Grossly, the tumors appeared as reddish-brown, lobulated, and fairly well-encapsulated nodules. The average size was 3.5 cm in diameter, with extremes of 2 and 10 cm. In six cases, the material contained segments of the carotid vessels, and in four of these cases the vessels tunneled through, and were inseparable from tumorous tissue. In four other cases the neoplasm did not appear to be well encapsulated, and there was gross evidence of invasion of the surrounding tissue. Unfortunately, only one specimen had been preserved in Zenker's solution. This specimen was stained a light orange by the chromium salts. Nineteen tumors were unilateral, one was bilateral.

Microscopic frozen-sections stained with hematoxylin and eosin presented, with the low-power objective, two rather characteristic histologic patterns, alone or mixed. One we shall designate, for the sake of simplicity, as the "alveolar" or "insular" pattern, the other, as the "peritheliomatous" pattern. Eight of the 20 tumors had an alveolar pattern, the remaining 12 tumors had a peritheliomatous pattern.

In the alveolar, or insular, pattern, large islands of pale polyhedral cells appeared to be separated by narrow bands of connective tissue without much hyalinization. The epithelial-like islands of tumor cells occupied more than 95 per cent of the region enclosed by each field, as viewed with the low-power objective (Fig 1a). Here and there the fibrous tissue was separated to permit the passage of large, thin-walled vascular sinuses which frequently were encroached upon by budding masses of tumor cells (Fig 1a). A thin mantle of endothelial cells seemed always, however, to separate the tumorous buds from the actual lumens of the blood vessels. Old blood pigment was generously distributed throughout the stroma in four of the eight tumors in which this alveolar pattern was predominantly observed (Fig 1a).

In the peritheliomatous pattern the cellular units, although they were somewhat alveolar, were much smaller and more irregular than they were in the insular pattern. The usual picture was that of small clumps of cells arranged in nests, or irregular strands which were separated from each other by very vascular connective tissue (Figs 1b and 2a). In some portions these clumps of cells were seen to surround vascular sinuses. The blood vessels were everywhere abundant, but varied in size, being on an average smaller than those observed in the alveolar pattern. Hyalinization of connective tissue was a prominent feature in the peritheliomatous patterns—the tumor being

sometimes replaced by such hyalinization to a degree seen usually only in connection with mixed tumors of the salivary glands (Fig 2*b*) This hyaline, fibrous tissue showed a tendency (as observed by others) toward a distribution in the form of wide "bands" or "buds" (Fig 3*a*) Hemorrhage, old and recent, was observed in eight of the 12 tumors of the peritheliomatous pattern

Cytologically, regardless of the type, the tumors were seen to be composed mainly of polyhedral cells which had the following characteristics (1) A

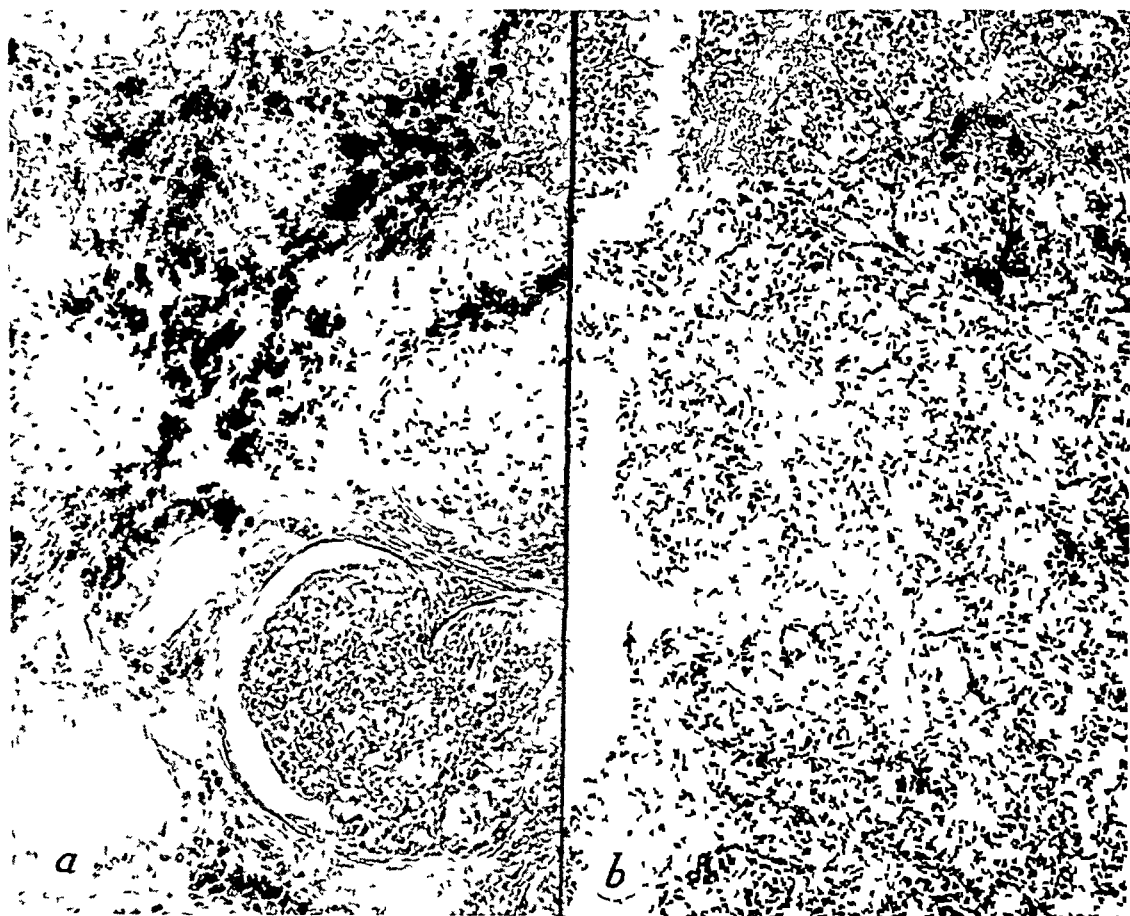


FIG 1*a*—Alveolar pattern in tumors of the carotid body, with large islands of tumor cells and occasional intravascular buds, a large amount of dark staining blood pigment can be seen (frozen section, hematoxylin and eosin, $\times 50$) (*b*) Peritheliomatous pattern in tumors of the carotid body in which small alveolar units of tumor cells separated by small capillary spaces can be seen (frozen section, hematoxylin and eosin, $\times 50$)

large amount of eosinophilic cytoplasm containing numerous vacuoles and granules so small as to be seen only with high magnification, and (2) one or more hyperchromatic nuclei

In uninucleated forms the nucleus was generally oval in shape, eccentric in position, and had a very sharply defined nuclear membrane (Fig 3*b*) Occasional "grooving" was observed, but did not appear to be characteristic The chromatin appeared to be condensed in small clumps connected by delicate strands seen only on careful focusing More than one nucleolus was the rule In multinucleated forms, the nuclei were usually congregated eccentrically in a large cytoplasmic mass Uninucleated and multinucleated giant cells were frequently observed, especially in the malignant tumors of the series

(Fig 4a and b) In cases in which an excess of hyaline substance was present, the tumor cells seemed to be partially involved in the process, the cytoplasm of such cells occasionally being fused with the surrounding hyaline material (Fig 2b), with the formation of intracytoplasmic hyaline "inclusion bodies." Aside from this type of degeneration, a second type frequently was seen in some portion of nearly every tumor studied. The nuclei in this latter type first became pyknotic and the nucleoli disappeared. At a little later stage all nuclear detail was lost and the nuclear membrane became very

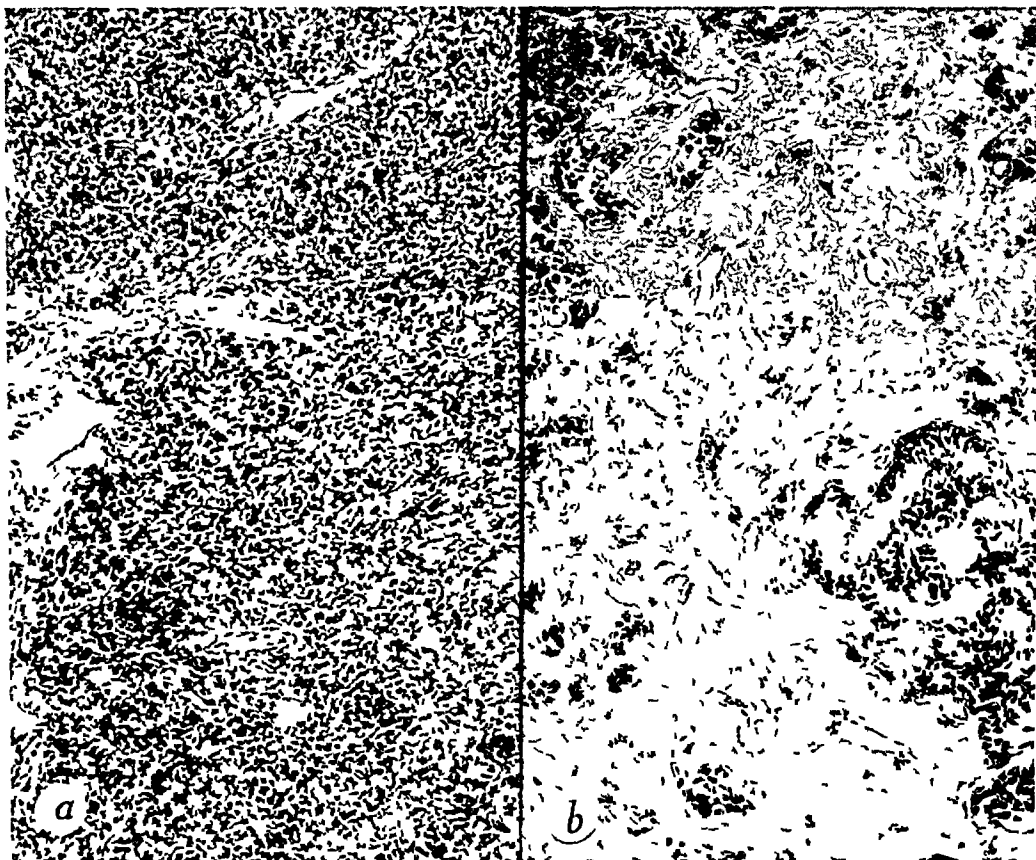


FIG 2a—Peritheliomatous pattern in tumors of the carotid body in which the intimate relationship of tumor cells to the vascular spaces is more evident than in Figure 1b (frozen section, hematoxylin and eosin, $\times 50$). (b) Extensive hyaline degeneration in a tumor of the carotid body in which the "epithelial" elements appear to fuse with the masses of collagenous and hyaline fibrous tissues (frozen section, hematoxylin and eosin, $\times 50$).

shrunk and "crinkled" (Fig 5a). At the same time the cytoplasm appeared to be swollen and somewhat basophilic, whereas the vacuoles were increased in size.

Very definite malignancy, as shown by active mitosis, cellular variation with giant cells (Fig 4a), invasion of capsule, and the like, was present in ten of the 20 tumors in this series. However, as compared to cells of the normal carotid body, all these tumors were composed of relatively undifferentiated cells. (Perhaps it would be well, on this basis, to regard these neoplasms as being low-grade malignant lesions possessing potential powers of,

if not actual tendencies toward, invasion and metastasis) Two patients died of questionable cerebral metastasis One of these patients, and an additional one, had definite local recurrence of the growth In neither of the two cases in which the patients died, however, was permission to perform necropsy obtained, and for this reason the problem of metastasis remains unsolved

Elements of endothelial and fibrous tissue made up the rest of the microscopic picture, with the exception of occasional nests of chronic inflammatory cells which were noted in several of the cases As previously stated, the endothelial cells varied considerably in number and in distribution A most inter-

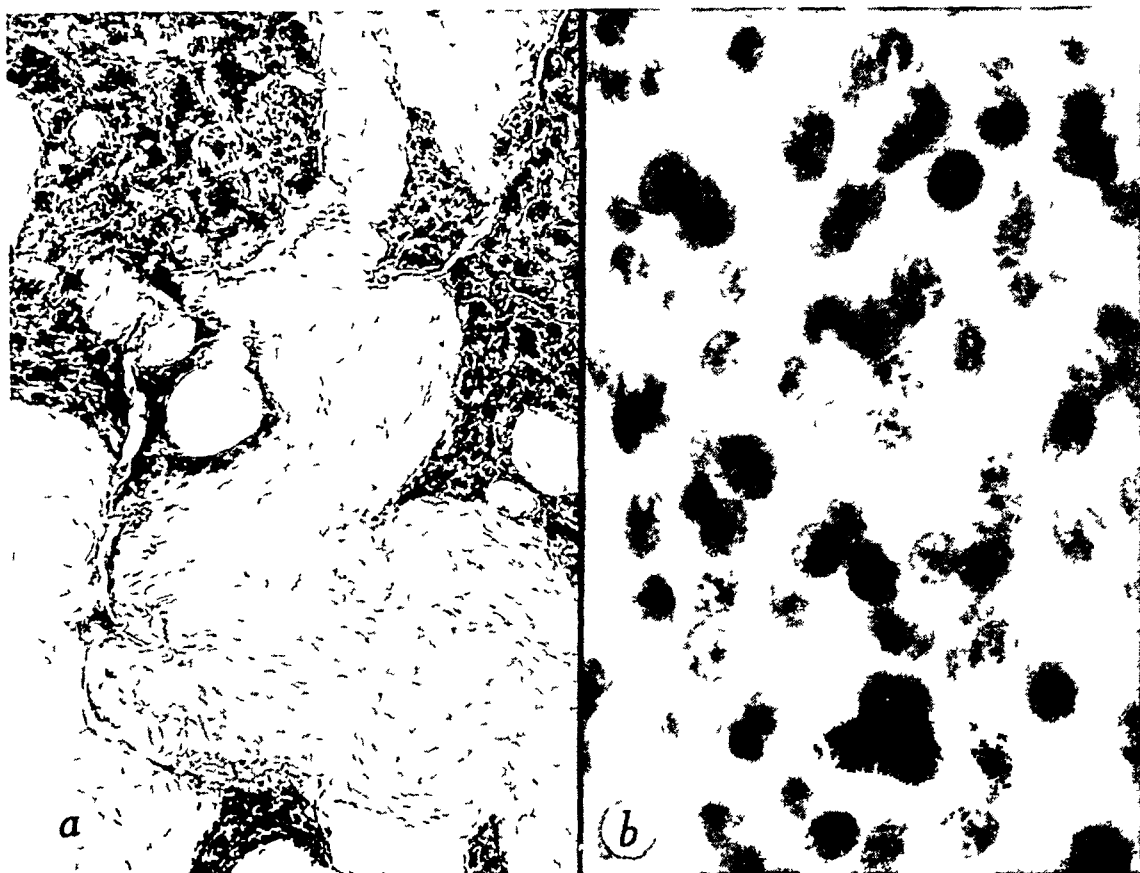


FIG. 3a—Hyalinization in a tumor of the carotid body, the characteristic "bands" and "buds" are clearly shown (frozen section, hematoxylin and eosin, $\times 50$) (b) Malignant tumor of the carotid body in which the oval eccentric nuclei, sharp nuclear outlines and the dense character and "speckled" distribution of the chromatin can be seen (frozen section, hematoxylin and eosin, $\times 900$)

mate approximation with tumor cells was observed in instances in which the neoplasm contained very vascular stroma On the other hand, when fibrosis and hyalinization were extensive, endothelial elements were not so abundant The degree of hyalinization bore no relationship to the duration of symptoms or age of the patient

Unfortunately, 19 of the 20 tumors had been preserved in a solution of formaldehyde, a circumstance which precluded study of the chromaffinity of the granular cells Various attempts at "rejuvenation" by means of subsequent fixation in Zenker's solution were made, but gave inconstant results However, in the single case in which a tumor had been preserved in dichromate

solution, the size and distribution of the chrome-positive granules appeared to be exactly similar to those of the granules in the polygonal cells seen in all the remaining 19 tumors (Fig 5b) It would appear, therefore, that the granules were identical in all of the 20 tumors of the carotid body

Incidence According to Age—According to reports in the literature, tumors of the carotid body occur among members of both sexes with about equal frequency In our series, however, 12 women and only seven men had this type of tumor Apparently, no person in any age-period is exempt The youngest

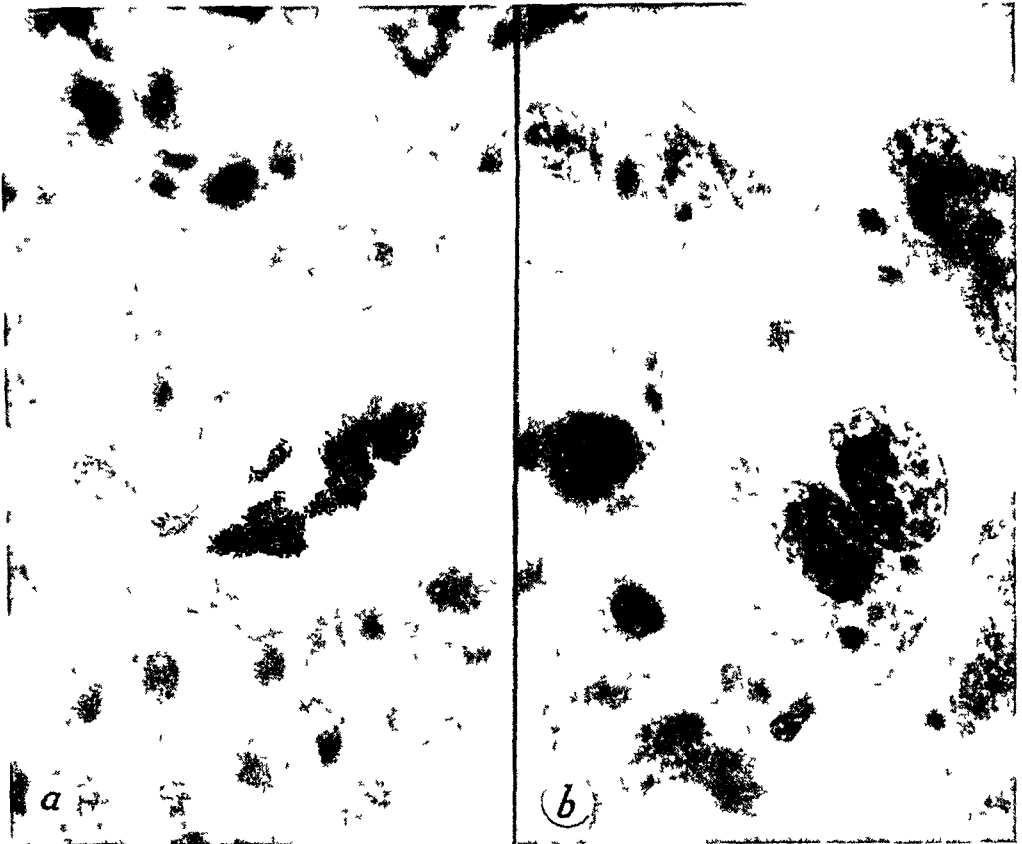


FIG 4a—Tumor of the carotid body in which multinucleated giant cells with pyknotic nuclei can be seen, in other uninnucleated tumor cells in other parts of the microscopic field a similar type of degeneration is visible (frozen section, hematoxylin and eosin, $\times 1000$) (b) Malignant tumor of the carotid body in which hyperchromatic eccentric nuclei, multiple nucleoli, sharp nuclear membrane and granular vacuolated cytoplasm can be seen as well as several uninnucleated and one multinucleated giant cell forms (frozen section, hematoxylin and eosin, $\times 500$)

patient in the cases reported in the literature was seven years old, and the oldest was 73 years of age The great majority of such tumors occur among adult persons, however, and according to Bevan and McCarthy,³ in 70 per cent of the cases the patients are from 40 to 60 years old In our series, the ages of the patients were as follows Two patients were 20 to 29 years old, six patients were 30 to 39 years old, four patients were 40 to 49 years old, five patients were 50 to 59 years old and two patients were 60 to 69 years old The average age of the 19 patients was 45.1 years

The tumors are usually unilateral but bilateral tumors have been reported by

Lund,¹⁰ de Tarnowski,²⁰ and Chase,⁴ and in one of our series of cases the tumor was bilateral. The tumors occur with equal frequency on each side of the neck. In our series, which includes 19 patients, nine tumors occurred on the left, nine tumors occurred on the right, and one was bilateral. Inclusion of the bilateral tumor thus brings the total number of tumors to 20, as afflicting 19 patients.

Symptoms—Tumors of the carotid body usually manifest themselves as painless, unilateral, slow-growing tumors situated in the superior, anterior

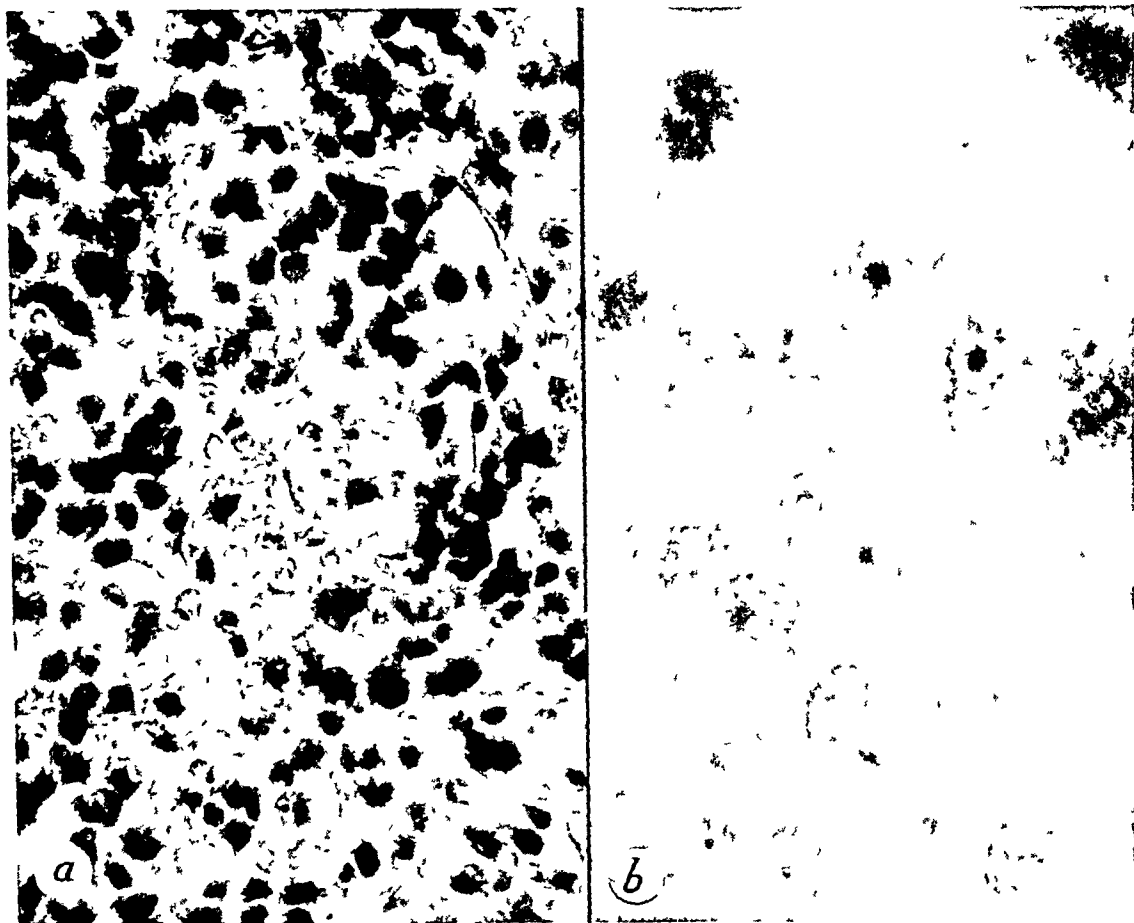


FIG 5a—Tumor of the carotid body in which "pyknotic" degeneration of the nuclei is shown (frozen section, hematoxylin and eosin, $\times 500$) (b) Section of tumor of the carotid body as freshly impregnated with chromate solution, the finely granular character of the cytoplasm is apparent (frozen section, hematoxylin and eosin, $\times 1000$)

cervical triangle, pushing out from under the border of the sternocleidomastoid muscle. They are ovoid or round, firm but elastic tumors and, because of their vascularity, can be compressed and temporarily reduced in size. They are deep-seated tumors and are never attached to the skin. These tumors usually have some lateral mobility, but since they are attached to the carotid vessels, they have little or no vertical mobility, and this latter characteristic has been noted by many observers as an important diagnostic point. Occasionally a bruit or thrill can be elicited, but this is not a constant observation. Often, a transmitted pulsation from the carotid arteries is evident, but it is important not to confuse this pulsation with expansile pulsation of an

aneurysm Compression of the carotid artery below the situation of the tumor will abolish the pulsation, bruit or thrill and often will cause some diminution in the size of the tumor

Tumors of the carotid body often are without symptoms other than gradual increase in size They have usually been present for some time before the patient consults a physician In our series, the tumor had been present before operation for periods of from one to 15 years, the average duration was about 5.7 years Peterson and Meeker¹¹ have reported that in their series

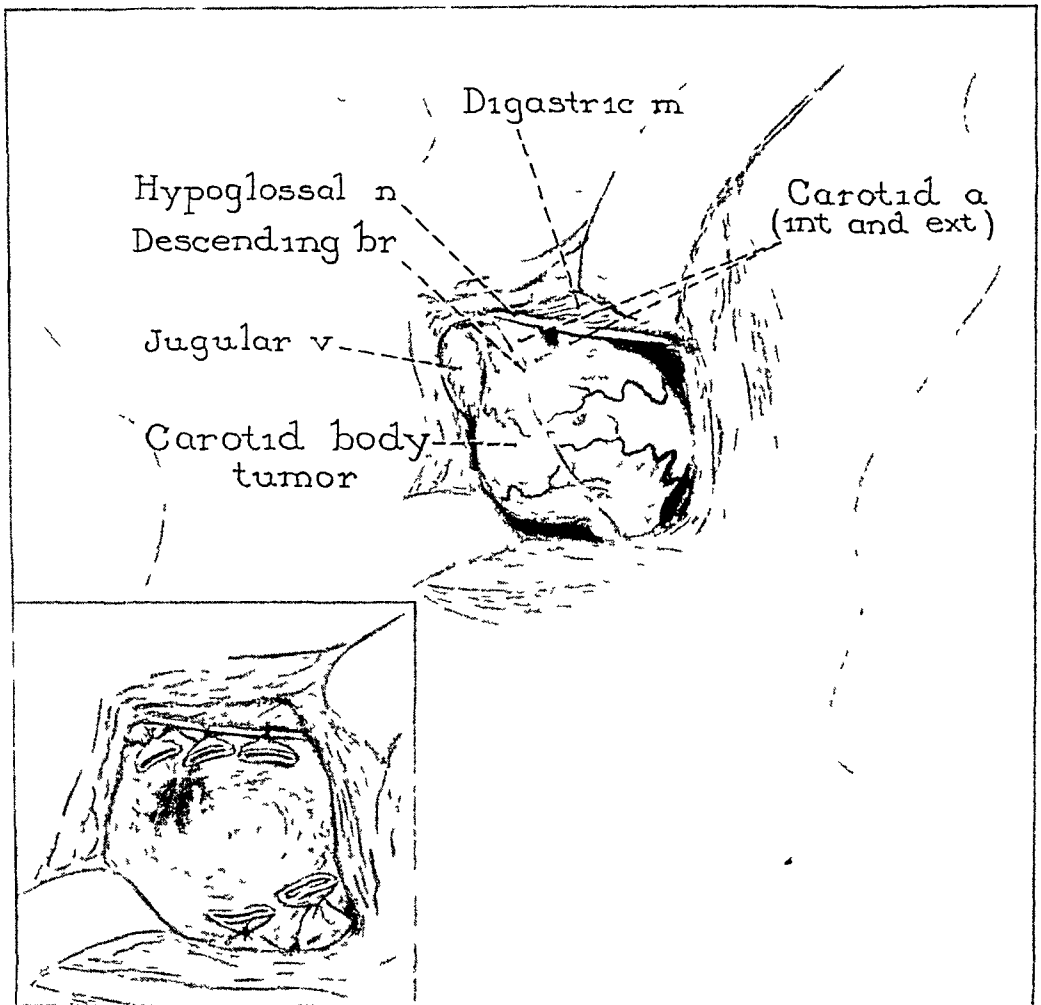


FIG 6—Artists' conception of exposure for removal of a tumor of the carotid body and of ligation of vessels

the tumor had been present for about six years before operation When tumors of the carotid body produce symptoms, such symptoms usually are caused by invasion or compression of important regional structures such as the vagus nerve sympathetic or recurrent laryngeal nerves, or the pharynx or esophagus Episodes of fainting, Adams-Stokes syndrome, hoarseness, dyspnea, dysphagia, cough, tinnitus aurium and headache have been reported as being symptoms referable to tumors of the carotid body and have been

attributed to compression or irritation of the vagus nerve. Horner's syndrome, exophthalmos and mydriasis have been reported, and have been attributed to disturbances in the cervical sympathetic nerves. Local, cervical or occipital pains have been held to be referable to involvement of the cervical plexus. In our series of 19 patients, only four complained of symptoms other than the increasing size of the tumor. One patient complained of a burning sensation in the throat, one of dizziness and episodes of fainting, one of paroxysmal pain in the neck and one of dysphagia and a sensation such as might be caused by an object lodged in the throat.

Diagnosis—In almost every report concerning tumors of the carotid body, it has been observed that the correct diagnosis rarely has been made preoperatively. Absence of such a preoperative diagnosis probably resulted from the fact that the tumor is so rare that the possibility of its presence is not even considered by the examining surgeon. The first correct preoperative diagnosis recorded in the literature was made by Klopfenstein,⁷ in 1895. Phelps, Case, and Snyder¹⁵ found that, in the series of 159 cases they reviewed, a correct preoperative diagnosis of tumor of the carotid body had been made in 12 cases and had been considered in 14 others. In our series of 19 patients, the correct diagnosis was made preoperatively in three and existence of a lesion of the carotid body was considered as a possibility in two other instances. According to reports in the literature, the most common erroneous diagnosis has been tuberculous adenitis. In our series a diagnosis of branchial cyst was made in six cases. In two of our cases the preoperative diagnosis was aneurysm. Such a wide variety of lesions may occur in the region of the neck affected by the tumors in question that making of differential diagnosis is extremely difficult, and it is often impossible to make it until histopathologic examination of the tissue has been carried out. Diagnosis of a tumor situated in this region must include a consideration of all the various types of cervical lymphadenopathy, carotid aneurysm, metastatic carcinoma, aberrant thyroid gland, branchial cyst, branchiogenic carcinoma, neurofibroma, ganglioneuroma and tumor of the carotid body. Aspiration, or the obtaining of specimens of tumors in this region by the punch-technic has been suggested as a means of securing material for microscopic study, which would aid in the differential diagnosis of cervical tumors. We feel that the vascularity of many of these lesions and their proximity to the great vessels of the neck make such methods dangerous, and we do not recommend them. Granted that tumors of the carotid body are rare and that differential diagnosis is difficult, we believe that the possibility of tumor of the carotid body must be considered in the presence of any painless, slow-growing tumor situated in the superior, anterior cervical triangle, particularly if the characteristic signs, as previously mentioned, of lateral without vertical mobility, and decrease in size of the tumor with compression of the carotid vessels, can be demonstrated. Clinical suspicion of tumor of the carotid body necessitates careful evaluation of the surgical problem presented and permits proper preliminary treatment, so that the danger of the patient's death from cerebral anemia can be averted, or so

that paralyses or hemiplegia, should sacrifice of the carotid vessels be necessary to extirpation of the tumor, can be avoided

Treatment—It is now generally agreed that the ideal treatment of patients who have tumor of the carotid body is complete surgical removal of the lesion when this can be accomplished without sacrifice of the carotid vessels. Absolute agreement does not exist concerning those cases in which ligation of the carotid vessels is necessary for completion of the operation. Some surgeons, notably Bevan and McCarthy,³ have voiced the opinion that in those cases in which surgical exploration has shown the tumor to be inoperable without sacrifice of the carotid vessels, the incision should be closed, as would be the case after an exploratory operation, and the patient should be treated with radium and roentgenotherapy. We find little in the literature to indicate that roentgenotherapy and radium have been used in the treatment of tumors of the carotid body with much success, and Phelps, Case, and Snyder¹⁵ have reported seven cases in which patients were treated by roentgenotherapy and radium without appreciable benefit. We have used both these agents in conjunction with surgical intervention very satisfactorily, but we believe that if the treatment is limited to exploration with subsequent application of radium and roentgenotherapy, cure will not result in the great majority of cases. Furthermore, it has been our experience that if the surgeon explores the lesion sufficiently to determine definitely whether or not the tumor is attached to the carotid vessels, it, usually, will be necessary to complete the removal of the tumor, even if it requires sacrifice of the carotid vessels to control the bleeding arising from these very vascular tumors. Finally, we believe that complete removal of the tumor is indicated, even if sacrifice must be made of the carotid vessels, because all such lesions in our experience have been either malignant or potentially malignant. They rarely recur or metastasize after complete removal, and the results obtained among those patients who have survived the operation are very satisfactory. In our series, there were only two cases in which local recurrence of tumors occurred, and one of the patients so affected lived for eight years, and the other for ten years, postoperatively. Peterson and Meeker¹⁴ reported five cases of local recurrence in the 18 cases they reviewed. In two of our cases distant metastasis was suspected, but we have been unable to find any proved instance of distant metastasis from tumors of the carotid body.

Although we advocate complete surgical removal as the proper treatment of tumors of the carotid body, this procedure is not one to be considered lightly or to be attempted by one whose practice is only partly surgical. The proximity of these tumors to the carotid vessels, the jugular vein, vagus, recurrent laryngeal, cervical sympathetic, hypoglossal and glossopharyngeal nerves must be appreciated, and the effect of injury to these structures must be evaluated. The operative mortality in cases of tumor of the carotid body, according to Phelps, Case, and Snyder, in the 159 cases they reviewed, was 24 per cent. They found, as have all other investigators in this particular field, that practically all the operative deaths occurred in cases in which

ligation of the carotid vessels had been necessary. In our series of 20 tumors involving 19 patients, there were four deaths, a mortality rate of 20 per cent, based on the number of tumors, or 21 per cent, based on the number of patients. The cause of each death was hemiplegia following ligation of the carotid vessels. It is interesting to note, in this connection, that, in our series, sacrifice of the carotid vessels was necessary in nine instances. The average age of the patients who died following ligation was 53 years, whereas the average age of those who survived ligation was 31 years. Two patients in the younger group were afflicted by transient hemiplegia which gradually disappeared. It has been our experience that in approximately one-half of the cases of tumors of the carotid body, ligation of the carotid vessels is necessary for complete removal of the tumor (Fig. 6). Because of the risk which this procedure entails, particularly for older individuals, we believe that in any case in which tumor of the carotid body is suspected, the patient should receive proper preoperative preparation consisting of systematic compression of the common carotid artery against the transverse process of the sixth cervical vertebra several times daily for a few weeks so that an attempt may be made to develop improved collateral circulation in the brain on the affected side. Compression should be carried out for gradually increasing periods until the patient can tolerate complete compression of the vessel for long periods without experiencing faintness or loss of consciousness. We believe that application of this procedure will result in a definite decrease in the risk of surgical intervention in these cases, particularly among older individuals.

Other structures that may be injured in the course of surgical removal of tumors of the carotid body are: The internal jugular vein, the vagus nerve, the recurrent laryngeal nerve, the cervical sympathetic chain of nerves, the hypoglossal nerve and the facial nerves. As previously noted in our series, ligation of the common carotid artery was necessary in nine cases, and in two additional cases the external carotid artery alone was ligated. In six cases the internal jugular vein was ligated. The hypoglossal nerve, the vagus nerve and the recurrent laryngeal nerve were injured in one case each in our series. Phelps, Case, and Snyder reported that in the series of 159 cases they reviewed, operative injury to structures other than the carotid vessels occurred in 24 per cent of cases.

In our series of 20 tumors of the carotid body, there were ten tumors which were classified as being definitely malignant, and ten that were classified as being potentially malignant. We have found no way to determine the nature of these tumors before microscopic examination was made. The duration of the tumor before operation was essentially the same in both groups. The necessity for ligation of the carotid vessels was practically the same in both groups. The number of immediate postoperative deaths was equal in both groups. We have traced the eight patients who had definitely malignant tumors, who survived operation, and have found that two died of recurrence eight and ten years after operation. The rest were alive and

well at the time of this report. One patient has survived 15 years and another 11 years. In the other group we have been able to trace only five patients, they are alive, and have been well for from one to 14 years after operation. One patient in our series received preoperative roentgenotherapy, elsewhere, without benefit. Four of our patients received roentgenotherapy postoperatively, three received radium postoperatively and one received both roentgenotherapy and radium therapy. We cannot prove, on the basis of observations in our series, that roentgenotherapy or radium therapy has been of definite value in the treatment of the disease in question, but we believe that either type of therapy is justified if it is used in conjunction with surgical intervention.

CONCLUSIONS

Tumors of the carotid body are relatively rare, but the possibility of the presence of one of them should be considered in any case in which a tumor occurs in the superior, anterior cervical triangle of the neck, particularly if lateral mobility without vertical mobility of the tumor is present, if there is transmitted pulsation of the tumor, and if the tumor decreases in size on compression of the carotid vessels.

Tumors of the carotid body occur with equal frequency among members of both sexes. The majority occur among persons who are from 40 to 60 years of age. They are usually slow-growing, painless tumors, and have been present for from six to seven years before the patient consults a surgeon.

Tumors of the carotid body are always malignant or potentially malignant tumors. They rarely recur or metastasize after complete surgical removal.

The treatment of tumors of the carotid body should be complete surgical removal. The operation is delicate and dangerous because of the proximity of the tumor to vital structures in the neck. Ligation of the carotid vessels is necessary for complete removal of the tumor in about 50 per cent of cases.

Ligation of the common carotid vessels constitutes the greatest danger of the operation. We believe that in every case in which a tumor of the carotid body is suspected, the patient should have proper preliminary treatment consisting of systematic compression of the carotid artery several times daily on the affected side for gradually increasing periods. This should be continued until the patient can tolerate complete compression for long periods without experiencing episodes of fainting or loss of consciousness. This procedure will help improve collateral circulation and will materially lessen the mortality and morbidity rate accompanying those operations in which ligation of the carotid vessels is necessary.

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THE SUCCESSFUL REMOVAL OF A SADDLE EMBOLUS OF THE AORTA, ELEVEN DAYS AFTER ACUTE CORONARY OCCLUSION*

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THERE IS NOW a moderately extensive literature on the clinical use of heparin¹ However, instances where the use of heparin has made possible the successful removal of large emboli are not numerous,^{2 3,4} hence, we are reporting such an occurrence

A physician, age 32, (Hosp No S-41624), ran up the 20 steps at the entrance of the Hospital of the University of Pennsylvania at 8 30 on the morning of March 28, 1939 He then felt some tightness in his upper sternal region and in both upper arms Shortly thereafter, while attending routine hospital duties he became weak and noticed more discomfort in his chest Then he experienced severe pain under the sternum and in his arms, broke out in a cold sweat, and felt as though he could not take a full breath He was put to bed and given 1/3 gr of morphine sulphate

When seen at 9 A M he had severe oppression in the lower sternal region and his arms felt heavy He was pale and sweating The pulse was 60, the blood pressure 130/90 Physical examination was otherwise normal Nothing unusual was heard in the heart or lungs The abdomen was soft and the extremities were normal

At first, the diagnosis was uncertain, but the following features made it quite clear that the patient had suffered a cardiac infarction in the anterior surface of the left ventricle (1) The electrocardiograms (Fig 1) showed findings which are quite characteristic of such a lesion, (2) the temperature rose to a high point of 103° F on the second day, and remained above normal for six days, (3) a definite pericardial friction rub was heard on March 29, 1939, and disappeared the next day, (4) a gallop rhythm was heard on March 31, 1939, (5) the leukocyte count on the afternoon of March 28, 1939, was 16,000 per cu Mm, with 87 per cent of polymorphonuclear cells

An interesting feature of the first week was the dyspnea⁵ which he experienced He breathed most freely and comfortably lying flat on his face with his head turned toward the left All other positions gave him a feeling that he could not take a satisfying deep breath

The following features were at first difficult to reconcile with the diagnosis of cardiac infarction, but in the light of the whole situation must be considered as interesting variants of the typical picture, rather than as conflicting testimony (1) He was only age 32, (2) the pulse rate was 55 to 70 per

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minute during the first day, and never rose disproportionately to his temperature, (3) the blood pressure, which was 105/80 before the attack, rose to 130/90, remained at that level for the first three days, gradually dropped to 110/70 on the fifth day, and remained there, (4) on April 1, 1939 (the fifth day), a patch of consolidation (or atelectasis) appeared at the right base, and he coughed up some rusty sputum containing a few pneumococci. The temperature chart was not obviously affected by the pulmonary lesion. Three days later the temperature reached normal.

At 6 45 A.M., on April 7, 1939, the eleventh day following the cardiac infarction, the patient awoke with a feeling of formication in the scrotum. During the next three minutes the paresthesia extended down the inside of

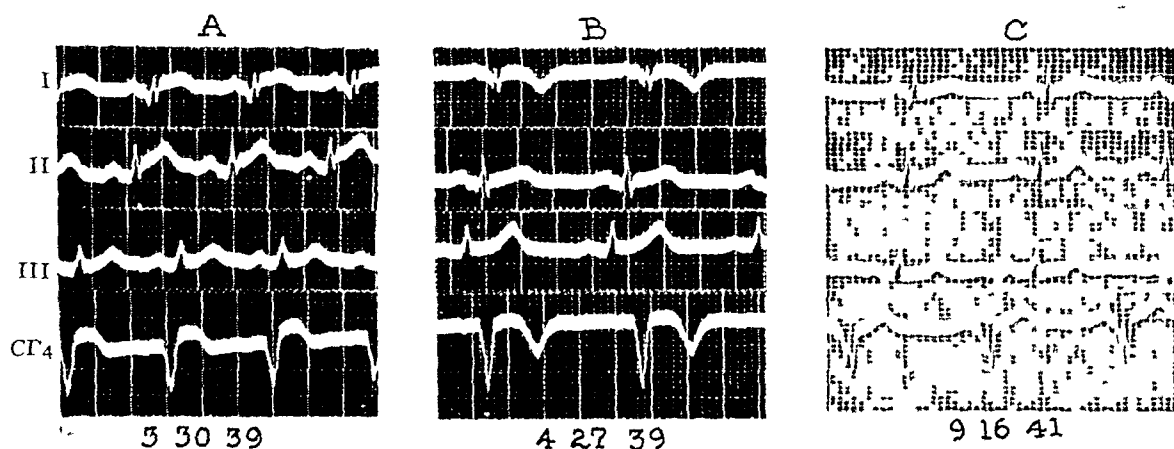


FIG. 1.—Electrocardiograms of patient described in text. (A) Tracing taken 3 30 39, two days after the onset. The RST interval elevations in leads I, II, and CF4 are characteristic of recent infarction in the anterior wall of the left ventricle. Lead CF4 also shows a Q wave. (B) Tracing taken 4 27 39, thirty days after the onset. The RST interval deviations have disappeared. T wave inversion is present in leads I and CF4. The contour of the tracing and the changes which have taken place since 3 30 39 are confirmatory evidence of former infarction in the anterior wall of the left ventricle. (C) Tracing taken on 9 16 41 showing further changes towards normal. The T wave inversion in lead I has disappeared. The Q wave in CF4 persists.

the thighs. Then it was replaced by agonizing pain in both legs. At this point the patient noticed coldness and mottling of both legs and himself made the correct clinical diagnosis. He recalled to his nurse a patient with cardiac infarction and an embolus to the bifurcation of the aorta whom they had attended together the year before, who subsequently had lost both legs and had died. After the patient had received a grain of morphine sulphate, the pain became bearable. When seen at 7 25 A.M., the penis and scrotum were anesthetic, the legs were cold, mottled, and anesthetic, and no pulses could be felt in or distal to the femoral arteries. There was no doubt that an intraventricular clot had been discharged and had blocked the aorta at its bifurcation (Fig. 2). Embolectomy was decided upon and he was taken to the operating room at 9 30.

The operation was performed by one of us (I.S.R.) under local anesthesia. A cannula was inserted into the left antecubital vein for intravenous fluid administration. Dr. J. H. Gibbon, Jr., measured the blood which was lost during the operation and controlled the rate of flow and amount of blood which the patient received. The distal end of the external iliac artery and

the proximal portion of the femoral artery of each side were exposed through a six-inch incision. In order to expedite matters, assistants were arranged for each side—Dis J E Rhoads and W D Frazier for the right side, and Dis N E Freeman and K A Zimmerman for the left. This greatly facilitated the operative procedures.

Two fine pieces of rubber tubing were placed beneath the vessels on each side proximal to the origin of the profunda femoris to prevent the clot, when dislodged, from passing distally, and to provide a method for hemostasis.

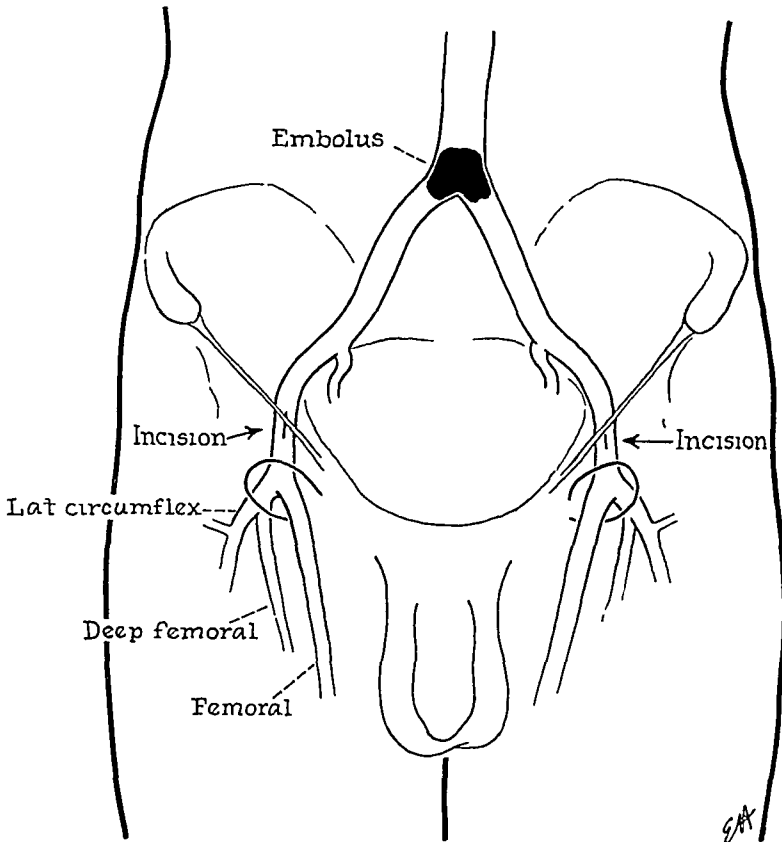


FIG 2.—Sketch showing position of embolus and incisions for its removal.

When the artery on the right was incised in the longitudinal direction, a little bleeding occurred from the distal portion of the vessel. A modified Babcock vein-stripper (Fig 3) was then inserted proximally until the soft substance of the thrombus was encountered. The stripper was then moved upward and downward in order to fragment the clot. When the stripper was withdrawn, free bleeding was obtained. A specially prepared catheter, the tip of which had been removed and the end carefully smoothed, was inserted toward the heart. After it had been introduced for approximately 30 cm suction was applied and the catheter carefully withdrawn. It carried with it several masses of clot. Free bleeding was prevented by traction on the proximal rubber sling.

A similar procedure was carried out on the left side. There was prac-

tically no bleeding on this side when the artery was first incised. A catheter was introduced and a small amount of clot sucked out. A free flow of blood, however, was not established until a vein-stripper had been introduced and pushed well up several times. A considerable amount of clotted blood was drawn down and a free flow established after the artery had been sucked out once more. A final attempt to draw clotted material out of the artery was made with flexible grasping forceps but no other clot could be found. The right artery was again sucked out.

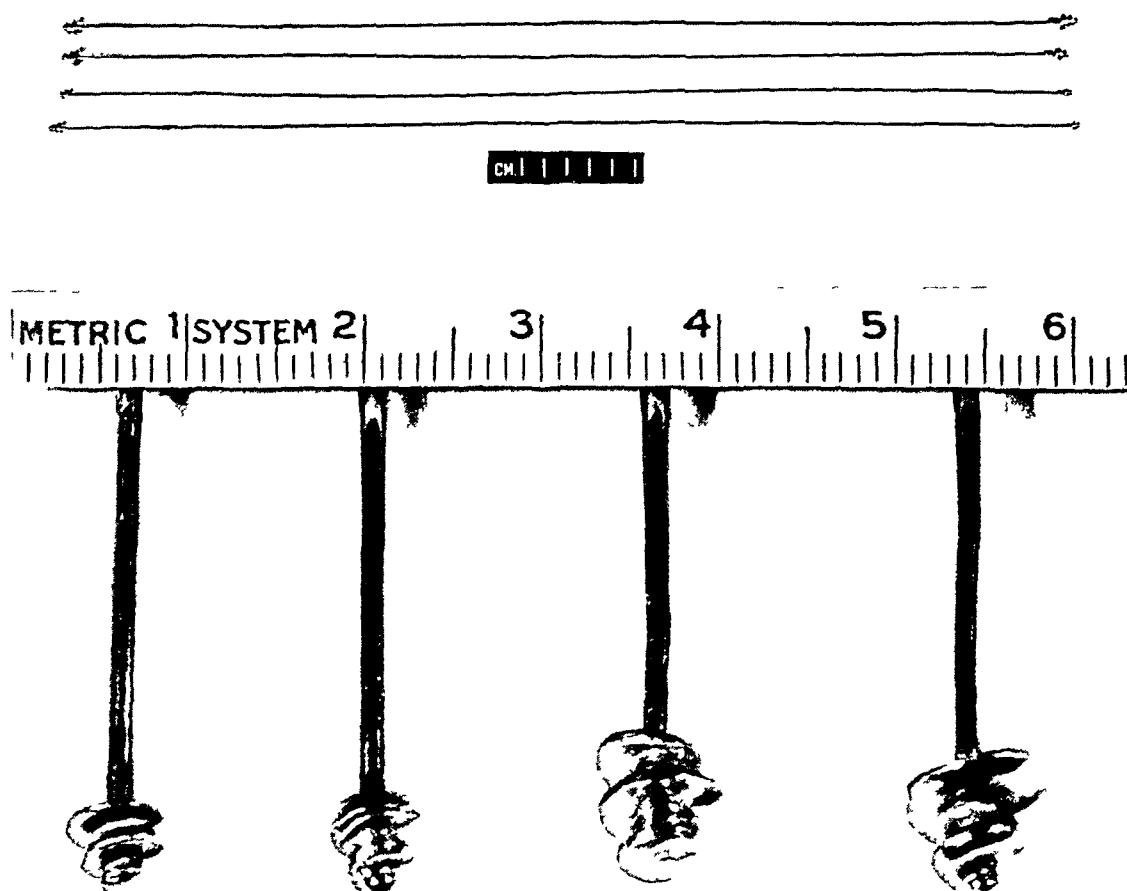


FIG. 3.—Modifications of the Babcock vein stripper for use in fragmenting an embolus

After a good flow of blood was obtained on both sides, the two arteries were closed with arterial silk, a double layer of continuous suture being used. Just as the suture line in the right femoral artery was nearing completion, 5 000 units of heparin (Connaught Laboratories) were introduced intravenously. Blood loss was compensated quantitatively by transfusion, the amount of blood lost being estimated by collection in a trap on the aspirator and a liberal allowance being made for blood removed on sponges.

After the last arterial suture was placed, an additional 5,000 units of heparin were given. The wounds were then closed in layers, the skin edges being approximated with interrupted black silk sutures. Despite his recent cardiac infarction, the patient stood the operation well.

Shortly following the operation, Dr. Norman E. Freeman did a left paravertebral injection with 1 per cent novocain.

Heparin was given for 11 days following the operation. Three types were used: Swiss, Swedish, and that made by the Connaught Laboratories in Toronto. It was given intravenously by the slow drip method by adding it to solutions of normal saline and 5 per cent glucose, or to 5 per cent glucose alone. The coagulation time as determined by the Lee-White method⁶ varied during the period of therapy from 14 minutes to one hour and 13 minutes.

Although no peripheral pulses were palpable in either lower extremity immediately after operation, the color and temperature of the right leg and its motion and sensation returned to normal almost at once. On the left side, some coldness and mottling remained, especially on the dorsum of the foot. Moreover, this extremity remained very painful below the knee, and showed loss of touch sensation in this area for several days. Evidently a small embolus had escaped below the site of exposure of the artery. Suction and pressure therapy employed at intervals on this extremity under the direction of Dr. Hugh Montgomery. However, for some weeks, an area of painful erythema remained on the dorsum of the left foot.

By May 15 the patient was out of bed and was taking a few steps. He was discharged from the hospital on May 24, walking with a cane. Sensation was now practically normal in both legs. He still experienced some pain in the dorsum of the left foot, the result of a persisting ischemic neuritis.

He returned to work the latter part of September, 1939. In January, 1940, he was operated upon for acute diffuse suppurative appendicitis. The operation was performed under spinal anesthesia, and his convalescence was uneventful.

At present, September 15, 1941, the patient has perfectly normal lower extremities. The musculature is normal. He walks without obvious disability and is working full time. He is playing golf, climbing stairs, and practicing surgery without subcostal discomfort. Physical examination is entirely normal. The blood pressure is 120/80. The orthodiagram shows no cardiac enlargement. The electrocardiogram is shown in Figure 1 C.

This patient is an example of a rather remarkable recovery from a situation which at the time looked almost hopeless. He faced an appalling situation, was aware of its exact nature at all times, yet maintained the most superb morale throughout. This may have been a factor in his recovery.

Discussion—It is now 24 years since McLean⁷ in Howell's laboratory first isolated an active anticoagulant from liver. Howell, who played a minor rôle in the original work, later named this substance "heparin." In 1933, Charles and Scott⁸ showed that this substance was present in varying amounts in a great many tissues, the ox lung, liver, and skeletal muscle, in order of the yield obtained from them. As a result of their work, a pure

preparation of heparin for intravenous use in patients became available. Heparin for human use has been made during the past few years in Canada, Sweden, and Switzerland. An active preparation is now being prepared in this country.

Heparin may be given subcutaneously or intravenously. It is inactivated by the addition of minute amounts of protamine, a point of very great importance when one wishes to bring the coagulation time back to normal rapidly.

Because of the extent and intensity of the ischemia in the lower half of the body of the patient we have just reported, it is our belief that adequate circulation would not have been reestablished without embolectomy. However, three subsequent experiences with major arterial obstruction of the lower extremities have shown us that embolectomy is not always necessary. The use of three conservative measures: (1) Heparin to prevent distal propagation of a thrombus, (2) paravertebral sympathetic block to relieve vascular spasm distal to the arterial obstruction, and (3) suction and pressure therapy to promote circulation in the affected extremity, will bring about a satisfactory result in a certain proportion of these patients.

The decision as to whether to persist with conservative therapy, or to resort to operation, depends upon whether or not there is evidence of continuing improvement in the circulation. If this fails to occur, operation should be carried out, for after a period of three to five hours, changes in the intima at the site of the occlusion may result in further thrombosis, despite the use of heparin following closure of the vessel.

The success which was achieved in this patient was possible only because of the excellent aid given by many individuals, only a few of whom are mentioned in this report. We are indebted to Drs. Doane, Behrend, Sappington and Whipple, who furnished the initial supplies of heparin.

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REFLECTIONS ON GASTRODUODENAL SURGERY*

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HONOLULU, T. H.

SIXTY YEARS ago the first stomach operation was performed. During the past half century an immense amount of work has been done and a voluminous literature has accumulated on this important subject. It seems fitting that, at this Congress, the sixtieth anniversary of the first stomach operation should be commemorated in a modest way, by presenting a bird's-eye view of what has happened to the human stomach since 1879.

Some of us here to-day were youngsters on April 5, 1879, when the courageous French surgeon, Jules Pean, performed the first gastric resection for cancer of the pylorus. His patient lived four days and died of exhaustion. It was not until three years later that Billroth, in 1881, performed the same operation and acquired the distinction of doing the first "successful" operation of the kind—which has been known ever since as the Billroth No. I. But, his patient died in less than four months of carcinomatous peritonitis. It would seem in all fairness, as the immediate success of Billroth's operation was terminated by the death of the patient in a comparatively short time, that Pean ought to have some recognition and that the operation might properly be designated as the Pean-Billroth procedure. In the same year, 1881, young Antone Wolfier, 31 years old, thrilled at the idea of emulating his chief, the giant Billroth, attempted the same operation. He found the tumor fixed and the liver involved and was regretfully beginning to close the abdomen when Nicolodani, one of the assistants, whispered something in his ear. Wolfier picked up the jejunum, brought it across the front of the colon with a long loop and attached it to the anterior surface of the stomach, thus giving birth to gastro-enterostomy, an operation which has caused much joy and much suffering. Heineke, in 1886, and Mikulicz, a year later, working independently, devised pyloroplasty, and so in a space of a few years all the standard stomach operations were born.

The idea of side-tracking the malignant obstruction, first formulated by Nicolodani and carried out by Wolfier on that fateful day, September 27, 1881, was applied by Rydygier, in 1884, for a benign obstruction. Doyen, of Paris, in 1893, employed the operation for gastric ulcer without obstruction. This started a lot of trouble and the story of gastro-enterostomy is one of the most amazing chapters in the history of surgery.

In the early part of the century the furor of gastro-enterostomy spread over the surgical world. People with stomach ailments, real or imaginary, felt more or less in disgrace until they had had this operation performed.

* Read before the Third Congress of the Pan-Pacific Surgical Association, Honolulu, T. H. September 21, 1939.

House surgeons felt that they had not gained the goal of their ambition until they had undertaken their first gastro-enterostomy. It was a favorite subject of conversation at dinner parties. Not only was the operation employed where it was not needed, but it was often very badly performed. It is recorded that, needlessly, this anastomosis was performed in the following conditions: Functional disorders of the stomach, when the symptoms were due to other conditions such as appendicitis, gallstones, and tuberculosis of the intestines. Cirrhosis of the liver with hemorrhage, splenic anemia, tabes dorsalis, lead poisoning, prolapse of the kidney, colonic adhesions, epigastric hernia, and even vomiting of pregnancy.

It was bad enough to employ the operation where it was not wanted, but to perform it badly was adding insult to injury. It is recorded that the loop was made too short, the loop was made too long or that the loop was twisted. The stomata were badly placed, too near the pylorus and not at the most dependent part of the stomach. The stomach was attached to various parts of the small intestine and even to the colon. Some of the results were terrific. Hemorrhages, primary and secondary, vicious circle vomiting due to technical errors, internal hernia, and fixation by adhesions of the loop, were some of the disastrous sequelae and, in 1899, Braun first described "marginal ulcer." More than any other surgeons, Moynihan in England and W. J. Mayo in our country taught the profession how to perform the operation properly, and the adoption of Mayo's method of running the efferent loop downward and to the left reduced the number of twists and kinks.

Strangely enough, when gastro-enterostomy was born, a rather new disease appeared on the surgical horizon in the light of duodenal ulcers. Rokitsky, the great pathologist of Vienna of the last century, who, according to Geisler, is credited with having performed 30,000 autopsies, mentioned only hemorrhagic erosions of the duodenum, and Virchow wrote nothing at all on the subject. Ziemssen, in 1876, stated that "ulcer of the duodenum is a comparatively rare disease the proportion to gastric ulcer being hardly one to thirty." William Pepper of Philadelphia, in 1889, stated that not more than 70 authentic cases of duodenal ulcers had been reported. In our student days, the standard text-books mentioned duodenal ulcers only in their relationship to burns. Osler's Textbook of Medicine, 1899 edition, described duodenal ulcers with gastric ulcers and stated that "the duodenal ulcer is less common than the gastric ulcer." He also stated that it is more common in women than in men in the proportion of six to four. Little or no instruction on duodenal ulcers was given in the medical schools at the beginning of the century. Although some of the ulcers may have been missed, it does not seem possible that they were as prevalent half a century ago as they are now. The old fellows were keen observers and certainly would have found them had they been there. We now believe that the incidence of gastroduodenal ulcers predominates in the male sex in the proportion of four to one, that duodenal ulcers are ten times more common than gastric ulcers, and autopsy

reports state that ulcers or scars of ulcers are found in from 2 to 20 per cent of all postmortem examinations

The history of the technic of stomach operations is an interesting one. Moynihan records that, 50 years ago, he witnessed a pylorectomy for cancer in which 200 silk sutures were used to unite the duodenum and the stomach. In 1892, Murphy invented his famous button, which adorned every instrument table in the surgical world. I well remember 40 years ago, in the old New York Hospital, attending a clinic of Professor Robert F. Wen, in which he gave a laudatory lecture on the Murphy button concluding with the introduction "And now, gentlemen, I have the pleasure of presenting to you the inventor of this button." With that, a tall, distinguished looking man with a gray, closely cropped beard parted in the middle, arose from his seat in the amphitheater, bowed, and manifested his appreciation of the tumultuous applause of the demonstrative medical students of our day. The Murphy button taught surgeons facility in handling conditions in the abdomen. According to Moynihan "it gave a convincing demonstration of the essential simplicity of the process of visceral union. By using the button we learned how safely and how rapidly the peritoneal junction took place, there was no need, as it was now perfectly evident, for the hundreds of stitches that all surgeons were using. Firm, even approximation for a very few days would lead the button showed beyond a doubt, to a permanent and secure fusion of the opposed viscera. It is not the least exaggeration to say that Murphy revolutionized the methods of visceral anastomosis, and was partly responsible for giving that impulse to abdominal surgery, which in later years has carried it so far." After surgeons had learned the above quoted facts, the use of mechanical appliances had played their part. Moynihan further says "To Murphy, above all other surgeons, for his instrument is one of the most ingenious mechanical contrivances ever invented, we should gratefully acknowledge the debt we owe. Without the knowledge of his button, the surgery of the stomach and the intestines would never have reached its present stage." Poor Murphy, one of the most brilliant men of his time, a tremendously hard worker, died at the age of 59 of overwork and his button, which at one time was used all over the world, is not even mentioned in modern text-books.

Our experiences in gastroduodenal surgery here in Hawaii may be likened to a cross-section of stomach surgery since the days of Pean. The first gastro-enterostomy was performed in 1905. The first partial gastrectomy, Billroth No. II, was performed in 1908. In the same year, a gastro-enterostomy was accomplished without clamps. In the "hoise and buggy days," encountering an enormously dilated stomach with a contracted pylorus in a poorly equipped hospital, without any stomach clamps available, a posterior gastro-enterostomy was performed, and the patient made a very smooth recovery and went back to her position as a lei seller. I believe that she still functions in that capacity and may have helped to decorate some of you gentlemen on your arrival. At that time, there were many clamps, the Roosevelt, Little-

field, Scudder, Doyen, Haitman, Mayo-Robson, *etc*, and it was heresy not to use them. As I felt that I had committed a heresy, I kept quiet about it. At the same time, I was impressed by the ease with which the operation could be accomplished, and with the smooth convalescence of the patient. Since then I have rarely used clamps. In 1917, Rutheford Morrison, the brilliant English Surgeon, wrote as follows: "The greatest authorities advocate the use of clamps, and they offer many advantages. There is, however, a danger of internal hemorrhage after the operation has been completed, and although this may be a negligible risk in the hands of experts, it has so often occurred to my knowledge that, notwithstanding the most powerful advocacy to the contrary, I feel safer in doing the operation without clamps and tying each spouting vessel separately before completing the operation." If clamps are unnecessary, why use them? It always makes me shudder to see a nice, velvety piece of jejunum held like a vice in vicious looking instrument. I wonder what happens to the delicate tissues involved, if some of the tiny blood vessels are not crushed and the sympathetic nerves bruised and insulted. It is recorded that some marginal ulcers have appeared within two weeks of the operation. It is thus possible that this condition was aroused by the damage done by the clamps. Some gastro-enterostomies do not do well after operations. Balfour, in his monumental book, writes as follows: "In some cases, obstruction apparently may be complete and may persist even with discontinuing of food, lavage, or intravenous administration until for some unexplained reason the gastro-enteric stoma begins gradually to function and finally the difficulty is entirely corrected." May not this condition as above described be due to the physiologic resentment of the stomach and intestine against having been squeezed so tightly and so long?

In this most fascinating chapter of abdominal surgery, we have sat here on the sidelines and watched the contest going on, dashing into the fray now and then. In wondering what it is all about, we have tried to follow the voluminous literature on the subject and have concluded that there is hardly any disease which has so many causes as peptic ulcer. The different assigned causes may be divided into the category of predisposing and exciting. In the first group fall the so-called constitutional predisposition, the ulcer diathesis, the hypertonic stomach with active peristalsis, rapid emptying, hyperchlorhydria, hypersecretion, and along with this condition a relatively deficient blood supply of the ulcer area. The vessels supplying the lesser curvature are long and slender, and are mostly end-arteries going through the muscular layers to the mucosa. According to Alvarez, the mucous membrane of the lesser curvature is fastened to the muscle much as the skin of the palm of the hand is fastened to the fascia. Then there is adrenal overactivity, vagotonia, and the vasoneurotic diathesis.

In the group of exciting causes, there occur trauma, external and internal, from food too hot, too cold, and too rough, focal infections including diseased gallbladders and appendices, bacterial infections, preceding chronic gastritis and duodenitis, derangement of the nervous system, worry, fatigue, emotional

disturbances, organic brain disease such as tumors, alcohol and tobacco and of course, vitamin deficiencies and endocrine disturbances

Some writers have gone so far as to describe the physiognomy of the ulcer subject "with high malar prominences, a thin often wheezened face, an anxious look, poor nutrition, and an energetic demeanor." About 100 years ago, Dupuytren noted that duodenal ulcers sometimes developed after severe burns. Then this condition was described by Curling, in 1842. This is the one cause that all authorities agree on without controversy, and no one has satisfactorily explained the mechanism of it.

Like the coronary arteries, the ulcer producing portion of the stomach and the duodenum is subject to the great strain of wear and tear. The Germans called this area the "*magenstrasse*," and this part of the stomach may be thought of as a curving highway with a more or less continuous stream of automobiles passing over it. These automobiles vary in weight and speed. Erosions appear in the road surface and increase in size as they are subjected to added wear and tear. The pavement gives out and ulcers appear like chuck-holes of the roadway. The causes of the ulcer are as numerous as the different makes of automobiles passing over the highway.

With all the knowledge that has accumulated during the last 50 years, we have settled down to some definite conclusions and indications. History repeats itself. Over 70 years ago, Cruveilhier, whose name is still given in France to peptic ulcers, laid down the principle that peptic ulcers are curable, that dietary regimen is of paramount importance in the treatment and prevention of recurrence. He was also the first to recommend a milk diet. What can we conclude from the enormous mass of material and experience that has accumulated in the last 50 years?

(1) When Walter B. Cannon, in 1897, first gave a goose some bismuth to swallow so that he could study the process of deglutition, he started something which has been most valuable to the human race, and the roentgenologic diagnosis of stomach lesions is now over 90 per cent correct. Cancer of the stomach can be recognized early enough to be operated upon successfully.

(2) Ulcers can be cured by medical treatment in 50 to 80 per cent of the cases if the patient cooperates. Of patients treated in the earlier stages 85 to 90 per cent are curable. Essentials for a cure are lightening of physical and mental strain, a careful diet, and avoidance of alcohol and tobacco.

(3) What group of patients should especially not be operated upon? Young patients with small stomachs, small ulcers and hyper- or even normal acidity should not be subjected to gastro-enterostomy on account of the danger of jejunal ulcers. One of our patients had a profuse hemorrhage from a marginal ulcer following a gastro-enterostomy performed on the mainland 18 years previously, but this record has been superseded by Finsterer, who records a gastric hemorrhage 28 years after the primary operation.

(4) What patients should be operated upon? Those who have the following complications

- (a) Acute perforations of gastric and duodenal ulcers and the sooner the better
Should gastro-enterostomy be performed at the same time? No, unless, in exceptional cases, when the repair of the perforation produces a definite pyloric obstruction
- (b) Persistently recurring hemorrhage in spite of good medical treatment
In this connection, it is interesting to call attention to the radical revision of treatment of gastric hemorrhages by Meulengracht, who reduced the mortality of hemorrhagic duodenal ulcer to 1 per cent. In a series of 251 cases, the mortality with orthodox treatment in the same city for a similar four-year period was 79 per cent. Instead of starvation of the stomach plus transfusion, he feeds his patients meat balls, puréed vegetables, omelets, *etc.*, and allows them to eat as much as they want. In a few cases in which we have employed this treatment, we have been impressed by the results and believe that it is worth trying as the mortality from hemorrhage runs anywhere up to 16 per cent, according to different observers
- (c) Where pain persists in spite of good medical treatment, and the patient is becoming weakened from under-nourishment and suffering
- (d) Where there is organic pyloric obstruction not relieved by medical measures
- (e) In gastric ulcers where the possibility of malignancy can not be eliminated. This especially pertains to ulcers of the greater curvature

(5) What operations should be performed on the stomach when these conditions exist, and it is required that they be remedied? The stomach is a highly developed and sensitive organ and is very resentful of any liberties taken with it. Each case should be studied on its own merits, and unless the proper surgical procedure is applied to it there is bound to be trouble.

Gastro-enterostomy—An operation that carries with it the hazard of marginal ulcers supervening anywhere from 12 days to 28 years after its performance, should be looked at askance. The percentage of patients developing these ulcers varies in different reports from 3 to 40 per cent. Alton Ochsner thinks that 3 per cent is too low a figure and that an additional 25 to 30 per cent who have not been relieved by the operation, are sufferers from marginal ulcers.

(1) In ulcers of the lesser curvature, simple excision is condemned as producing a "lop-sided" peristalsis with impaired emptying and a gastro-enterostomy, in addition, is recommended. Fortunately, gastro-enterostomy in this group of cases is rarely followed by jejunal ulcer.

(2) In older people with marked pyloric obstruction, dilated stomachs,

and hypo- or anacidity, gastro-entriostomy is a satisfactory procedure. As time goes on and duodenal ulcers are recognized and treated earlier, perhaps there will be fewer patients in this group.

(3) In some cases of cancer of the stomach where a two-stage operation is advisable, gastro-entriostomy is indicated for the first stage.

With these three exceptions, we would say, "Don't do a gastro-entriostomy!"

For less severe cases, a plastic operation on the pylorus of the Heisley or Finney type, combined with excision of the ulcer, is far less apt to be followed by disagreeable consequences.

For severe cases with old, hard duodenal ulcers, fixed to the pancreas, subtotal gastrectomy is indicated with the removal of three-fourths to four-fifths of the stomach. In exceptional cases, the Billroth No. I and No. II and Devine's antial exclusion may be called for.

Time allows only a few minutes in which to mention our favored method of gastrectomy. Of the fourteen or more methods, we employ what is known as Moynihan No. II, as described in his admirable book on Abdominal Operations. The loop of the jejunum is carried in front of the transverse colon and attached to the cut end of the resected stomach, the loop running from left to right and not from right to left as in the original Polya. The proximal end of the jejunal incision is attached at the greater curvature and the distal part of the jejunal attachment is made at the lesser curvature. The cut end of the stomach may be partly closed or the jejunal attachment may be made along the full length of the resected area. This, I believe, is the method favored by Dr. Frank Lahey, although he calls it the Hofmeister operation. It is easy of execution, not complicated, does not involve opening the transverse mesocolon, and is usually followed by prompt reestablishment of gastric drainage with less disturbance and troublesome symptoms than follow more complicated methods.

LYMPHOGRANULOMA VENEREUM TREATMENT OF SEVERE CASES OF ANORECTAL TYPE BY A MUCOSAL-STRIPPING OPERATION^{*}

A PRELIMINARY REPORT

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It is only recently that lymphogranuloma venereum has become generally recognized as presenting a serious problem in public health, especially among the colored race. Statistical reports on groups of cases by the hundred are appearing almost every month in the literature^{3, 16, 17}. Figures emphasizing the frequency of the disease are given by Gray,¹ who found that out of 790 patients submitted to the Frei test in a city hospital in St. Louis there were positive reactions in 40 per cent of the colored patients, and 34 per cent in the white patients. Gray further found, as have others,² that a very large percentage of people who contract the disease entirely recover from it, and all that remains as evidence is the positive Frei test. Of those who do not symptomatically recover, and who go to the clinics for treatment, most of them will have the disease in a chronic form—their symptoms not being severe enough to require hospitalization. But not all the chronic cases will be so fortunate—a number of them will reach our hospital beds in a miserable condition. The patients are usually colored and they are destitute, therefore, one finds most of them in the charity hospitals. However, even at the Vanderbilt Clinic and Presbyterian Hospital in New York City, Dr. Helen Cuth and Doctor Gutman³ observed more than 200 cases of lymphogranuloma venereum during the period 1931–1938. They state: “The largest number of more than 100 were tertiary cases showing rectal strictures, chronic ulcerations of the genitals, elephantiasis swelling, proctitis, arthritis and systemic manifestations.”

Of the tertiary, or severe cases, we are at this time interested in those of the anorectal type. These usually have a rectal stricture, though some cases do not. The rectal stricture may vary in degree and extent, but in many cases intestinal obstruction of some degree exists. There are one or more abscesses, fistulae or sinuses about the ischioanal region. There are multiple condylomata about the sinuses and fistulae, and these condylomata are frequently at the anus and inside the rectum. Two of our cases had 18 and 20 fistulae, respectively, about the anus. Moreover, these patients are suffering from extreme loss of weight, a low grade fever, secondary anemia, secondary infection and frequently from other diseases, such as syphilis, carcinoma, or cardiovascular-renal disease³. They have pain from the local inflammatory process and pain in the abdomen from obstruction. In fact, what usually brings these

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patients to the hospital is the distressing local symptoms and the symptoms of intestinal obstruction. In a certain number the bowel perforates and the patient dies. Warthen⁴ states that practically every large series of cases has included fatalities from peritonitis. Gutman³ noted three such cases from the Presbyterian Hospital in New York, and, also, remarks that death following peritonitis is not rare. In some cases the disease progresses up the colon. Cases are reported with liver abscesses, renal involvement and systemic manifestations of various kinds.³

Once a case has become as severe as described, we find that he shifts from one hospital and clinic to another. This is because a satisfactory method of treatment is not available. Of our group of these severe cases, we find the history extending back over a period averaging four years.

Unfortunately for the patient the simple procedures do not always turn out so innocuously. Dilating the rectal strictures frequently only causes more scar tissue to form and eventually the state is reached where dilatation amounts to tearing and not stretching. With a colostomy of the ordinary loop-type, there is no reason why the disease cannot extend along the mucous membrane past the colostomy. After incision and drainage of the abscesses and fistulae, they are notoriously slow in healing, and, in fact, may not be expected to heal because of stricture, condylomata, and the disease existing inside the rectum. Frequently the proctitis apparently clears up, but often fibrous strictures of the rectum follow, and series of from 86 to 215 cases at a time have been reported.⁵ It is now thought that a great many so-called gonorrheal and luetic strictures of the rectum of the past were in reality due to the virus of this disease.

Some progress is being made in the conservative treatment. Cases successfully treated by diathermy and sulfanilamide have recently been reported.^{6, 7, 8} But it is one opinion that a certain percentage of these cases are going to require major surgical measures despite any medical treatment yet discovered.

The first surgical attempt to treat the disease was made by performing a simple loop-sigmoidostomy. The fecal current was thus shunted and the patient improved. Theoretically then, the symptoms might subside, and a re-establishment of the continuity of the bowel could be effected. However, we have operated on this assumption several times and have always been disappointed because the minute the fecal current passed down again through the old diseased rectum the local symptoms of infection and obstruction returned.

In chronic fibrous stricture without abscesses and fistulae, a local excision by the Whitehead type of operation has produced good results.⁹ Also, in this type of case, a plastic operation on the rectum by a posterior approach has given good results in a small number of such cases.¹⁰ ➤

Warthen reports ten cases of rectal stricture treated by obliteration of the cul-de-sac or rectovesical pouch and colostomy.⁴

At first, bold excision, of the abdominoperineal type, resulted in such a high

operative mortality that this operation was quickly abandoned. More recently, however, several cases successfully treated by this method have been reported.¹¹

Barber and Murphy¹² have reported 35 one-stage sacroperineal resections and 31 abdominal colostomies followed by sacroperineal resections. Their hospital mortality was 14.3 per cent.

Edwards and Kindell¹³ have reported six cases operated upon by the Lockhart-Mummery⁹ procedure. In all a loop-colostomy was first performed. One of their cases failed to survive the operation.

Our experience with these severe rectal cases has convinced us that the following points are true. The operative procedure must be undertaken in at least two stages, a colostomy has to be performed as a first step, an end-colostomy is better than the loop-type because the disease cannot travel upwards from the lower segment and fecal soiling of the lower segment is absolutely avoided. This colostomy will not cure the patient as the local process continues. The patient, however, will greatly improve and gain weight. The secretion of mucus from the distal segment is most annoying to the patient and adds to the number of daily dressings, also, the mucous membrane is a good medium for the virus of the disease. Any operation that opens into the peritoneal cavity during the excision of the lower segment is dangerous, and should be avoided because of the marked infection in the local lesions. The deep lymphatics and those of the mesentery and inguinal region are usually involved, therefore, even a block excision, as that of the abdominoperineal type, cannot remove all the disease. If the rectal dilatation has been carried out over a period of years, then the mucous membrane at the site of the stricture may be greatly damaged, otherwise the mucous membrane covering the rectal stricture may be intact. However, the mucous membrane below the stricture is commonly the seat of ulceration, condylomata, and multiple fistulae.¹⁴ It is possible, therefore, in some cases to remove the mucous membrane covering the stricture. Lastly, it is our experience, and the experience of others,¹² that after removal of the rectum and laying all abscesses and fistulae open to the air, they will completely heal. On these principles we have developed the following technic.

An end-colostomy is first established. This is essentially the same operation as the first-stage of Lahey's procedure for removal of carcinoma of the rectum.¹⁵ At this time we excise all of the sigmoid between the proximal and distal stomata. We do this because we find the colostomy functions better with a short pouch left inside the abdomen—the bowel empties better and there is less tendency to prolapse afterward. This type of colostomy separates the normal and diseased ends of the bowel a sufficient distance to prevent any contamination (Figs. 1 and 2). At this time any acute abscesses about the anal region are incised and drained because, in doing so, absorption is decreased and the patient is made more comfortable. The distal segment is irrigated twice a day with 2 per cent aqueous solution of mercurochrome (Fig. 2). This is the best of all the simple chemical solutions that we have employed.

Great improvement usually follows the first stage, so that, within a few weeks, the second stage of the operation may be performed. This stage may be described as a mucosal-stripping operation (Fig 3). An incision is made about the lower colostomy opening. The mucosa is identified and then stripped away from the muscularis and peritoneal layers by blunt dissection. This is accomplished with surprising ease. We have stripped, on two cases, 23 inches of mucosa without damaging the other layers and without enlarging the suprapubic incision (Fig 11). There are two reasons why this stripping can be so easily accomplished. First, the bowel behind one of these rectal strictures is

greatly hypertrophied, due to the years of back pressure and the effort of the bowel to force the intestinal contents past the stricture. This hypertrophied condition identifies the layers more definitely. Second, the blood vessels and nerves run along the muscularis and at intervals dip through the muscle layer and the loose submucosal tissue into the mucosal wall (Fig 10). These small, penetrating vessel branches do not bleed a great deal when divided. If a branch requires it, it may be ligated. After all the mucosa possible has been stripped from above, a small catheter or bougie is introduced in the tube of stripped mucosa and pushed

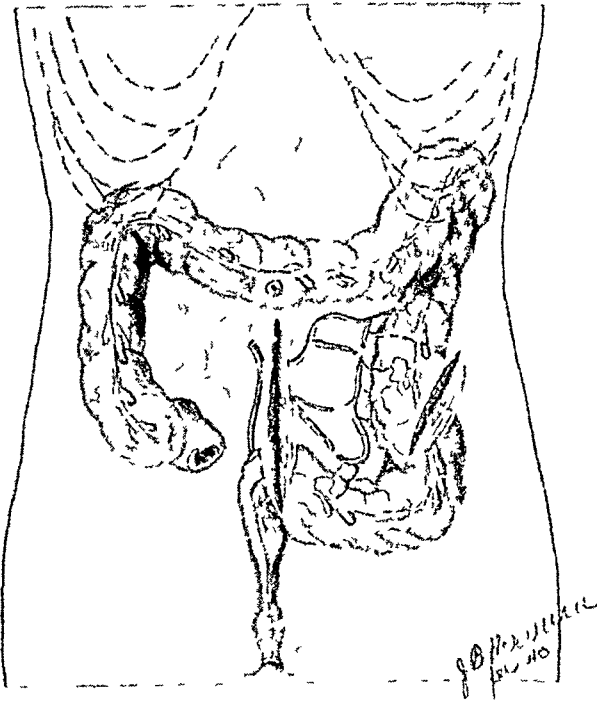


FIG 1—First stage of operation. Exploration of the abdomen through midline incision. Removal of most of the sigmoid as shown by dotted lines. Proximal stump of sigmoid brought out through left McBurney incision and distal stump brought out through lower angle of midline incision.

down through the rectum out the anus (Fig 4). The mucosa is then tied or sutured to the proximal end of the catheter. The patient is then placed in the lithotomy position. All surrounding condylomata and fistulous openings are, for the moment, not disturbed. An incision is made about the anus at the mucocutaneous junction, very much like the beginning of the Whitehead procedure (Fig 5). As soon as the mucosa is well-identified and freed, anterior and posterior incisions are made in the midline and the sphincter muscles divided and retracted laterally. The dissection is then carried to the levator muscles and, if necessary, these may be divided anteriorly and posteriorly. Meanwhile the rectal mucous membrane is further stripped by pushing the muscularis back from it (Fig 6). At this stage the anal end of the catheter is pulled downward, bringing with it the upper end of the mucosa—

LYMPHOGRANULOMA VENEREUM

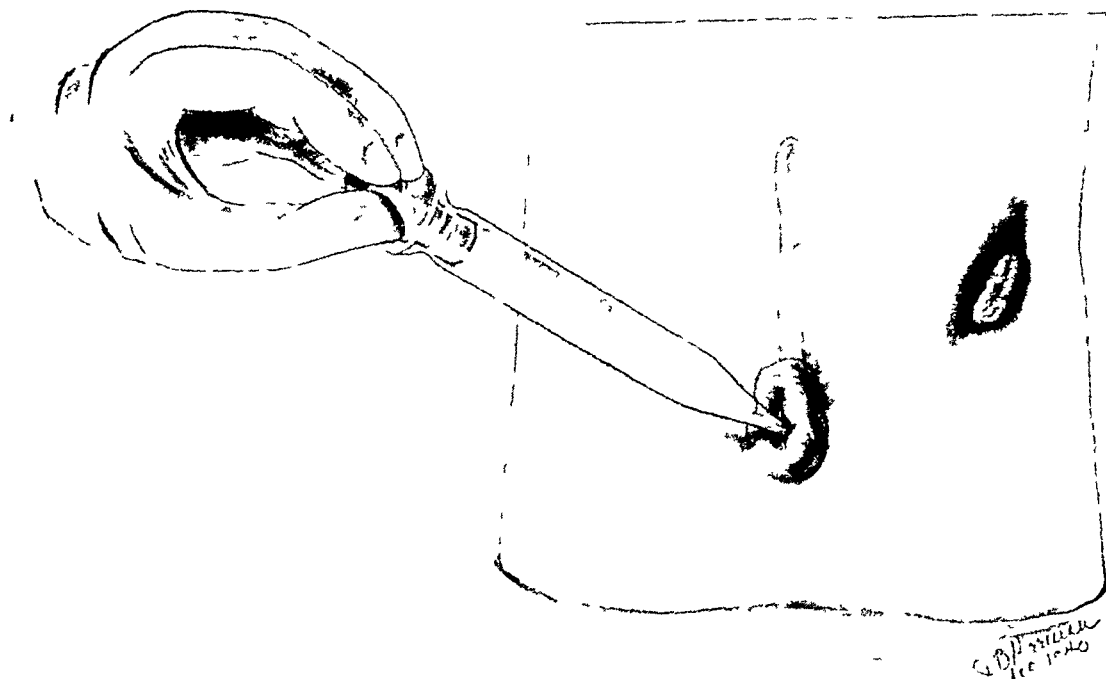


FIG 2—Left McBurney, permanent, short pouch, colostomy. Lower segment is irrigated twice daily, usually with aqueous solution of 2 per cent mercurochrome



FIG 3—Second stage, or the mucosal stripping operation. Usually performed two weeks or more after the first stage. Incision made about suprapubic colostomy. Mucous membrane identified and stripped out by pushing back muscular and peritoneal coats

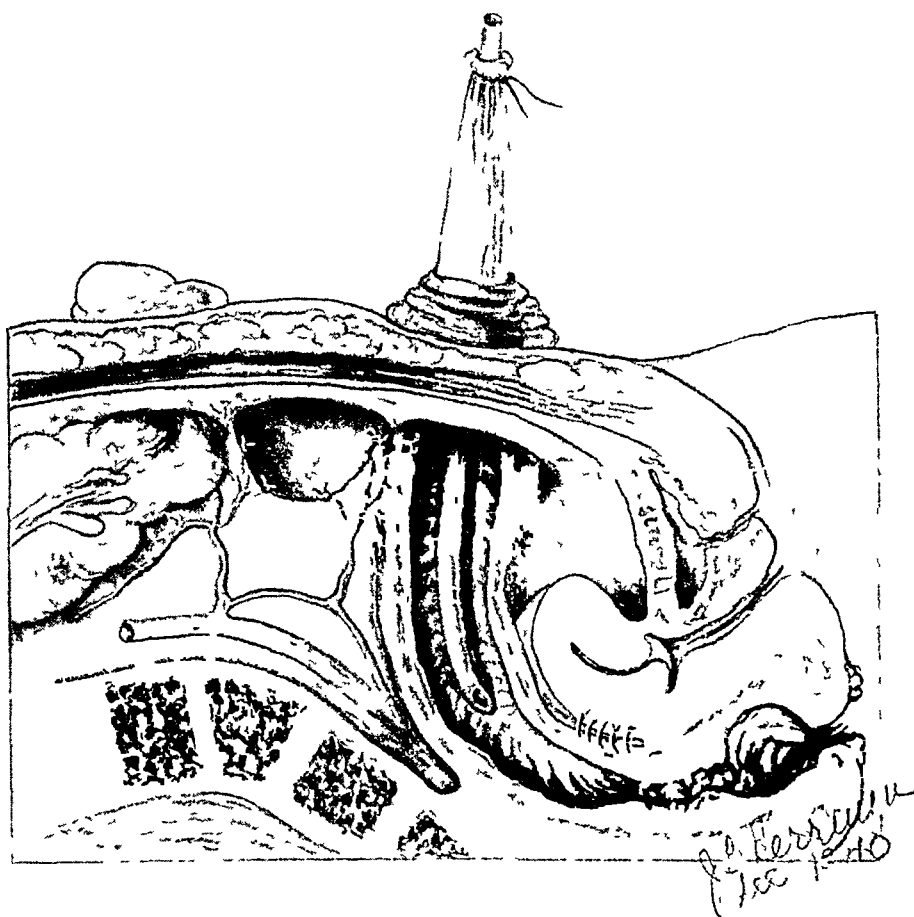


FIG 4—After all the mucous membrane possible usually ten to 20 inches has been stripped out above a catheter is introduced into the sleeve of mucous membrane and fixed by suture

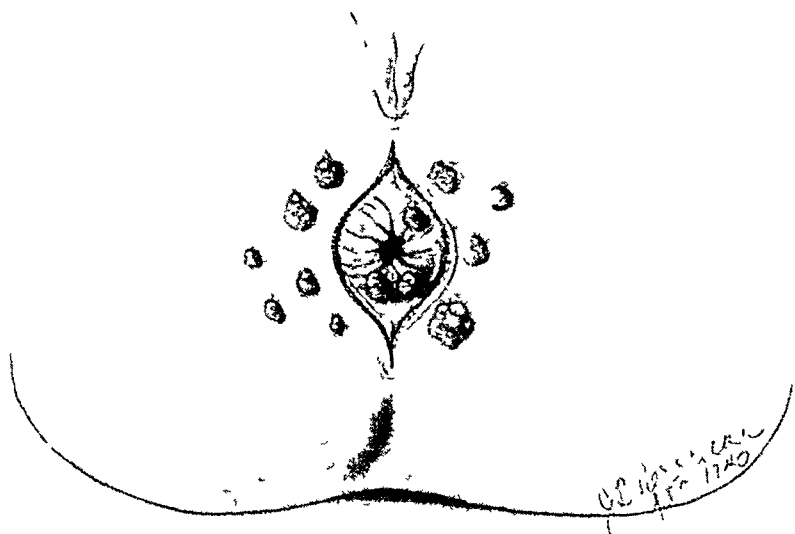


FIG 5—Patient put in lithotomy position Incision made about mucocutaneous junction of anus and dissection of mucous membrane begun Condylomata and fistulae for the moment, are left alone

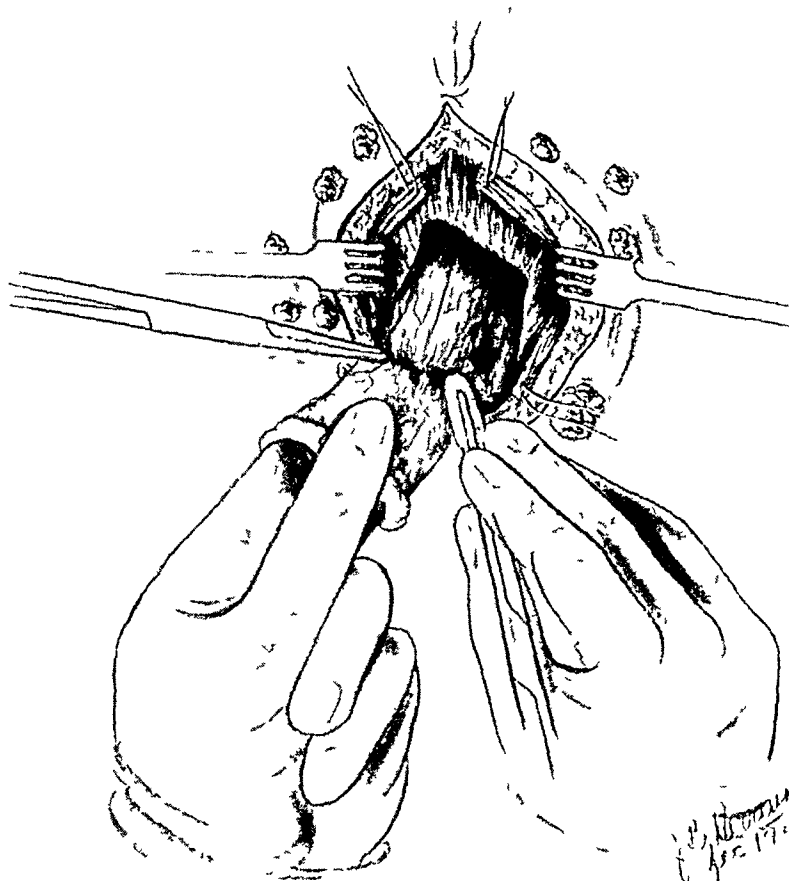


FIG 6—Mucous membrane being stripped out of rectum. Sphincters have been cut anteriorly and posteriorly, and retracted. Levator ani identified, and may be divided anteriorly and posteriorly if necessary.

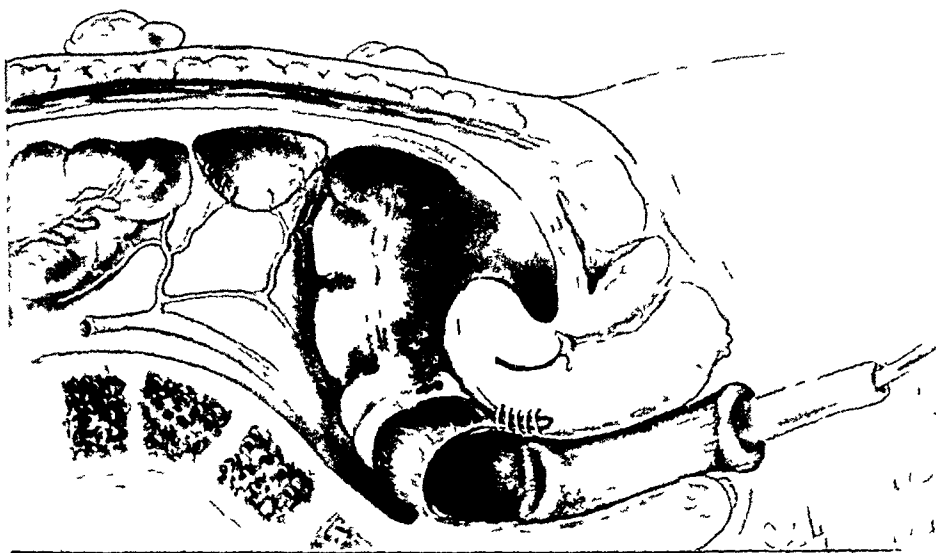


FIG 7—After the anal and lower rectal dissection has proceeded a few inches the catheter tip in the rectum is grasped and pulled out through the anus turning the sleeve of mucous membrane inside out. By further traction, and dissection if necessary, the whole sleeve of mucous membrane is delivered.

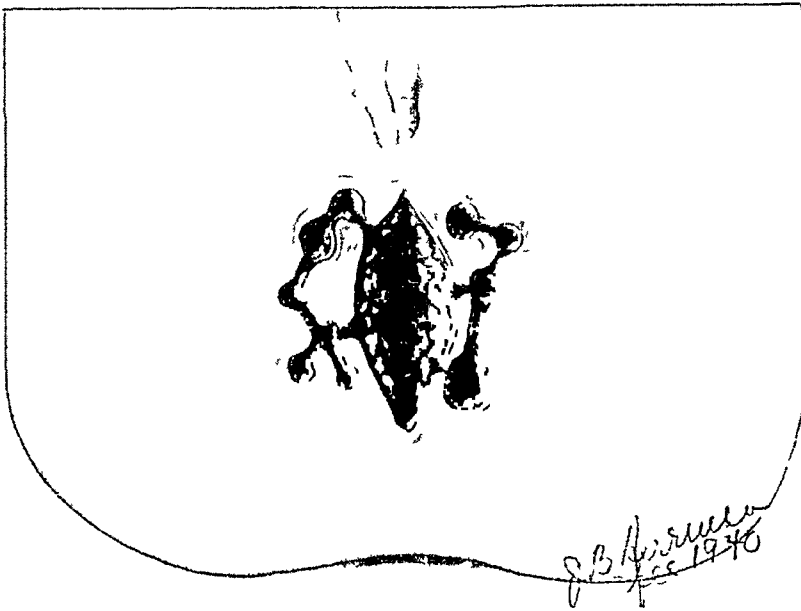


FIG 8—All fistulae are connected and opened wide. All condylomata are excised.

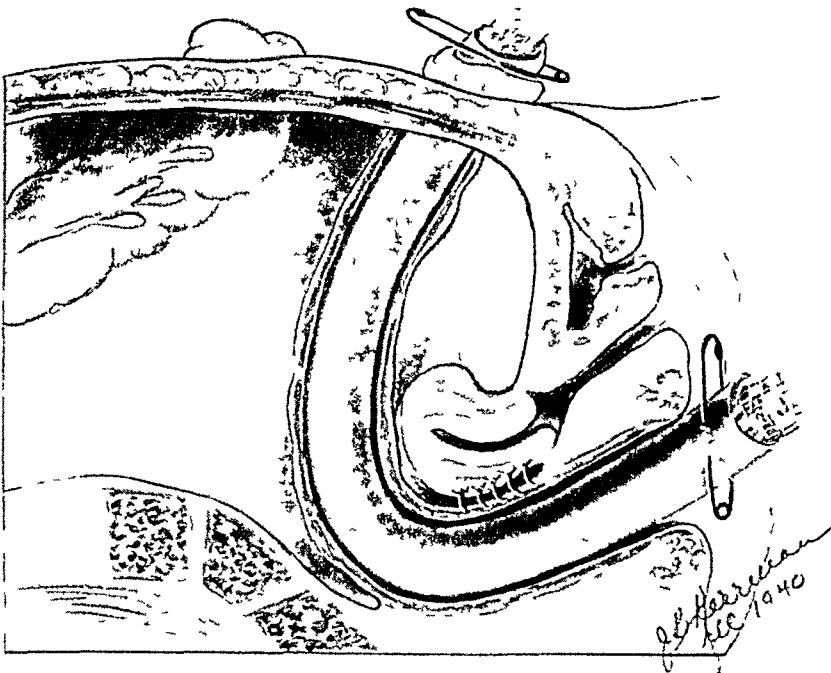


FIG 9—Drain left through from suprapubic to vaginal wound. The uterus is shown sutured to the rectal wall. This procedure of Warthen may be done at the first stage operation if desired. It gives an added factor of safety in this disease.

LYMPHOGRANULOMA VENEREUM

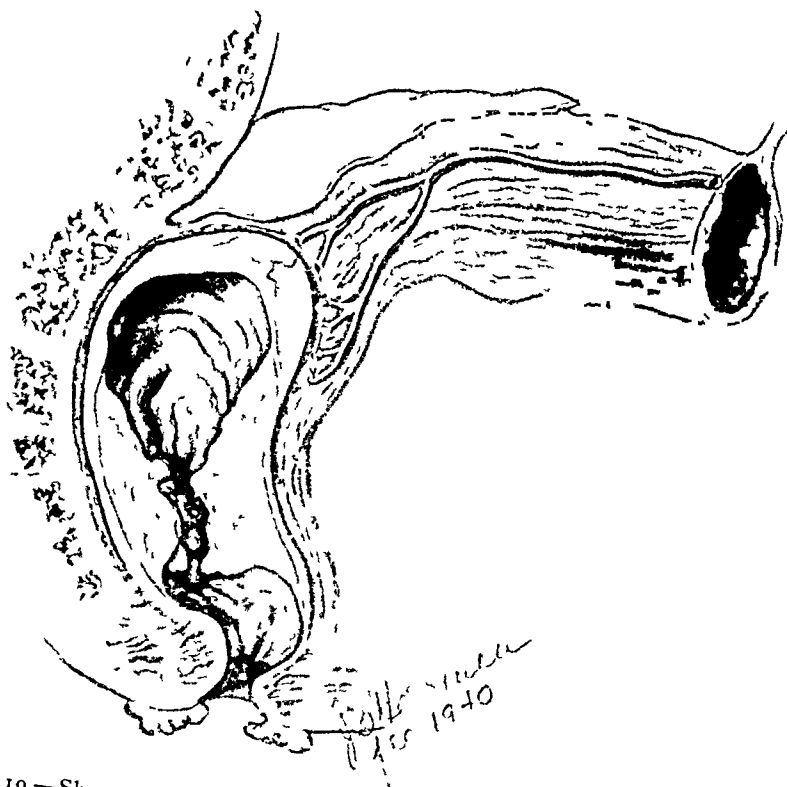


FIG 10—Showing that the blood vessels run between peritoneal and muscular coats. At intervals, small branches penetrate the muscle layer and then, after running along the submucosa, dip into the mucosa. The layers of bowel behind the stricture are easily identified because they are hypertrophied. Polypi, condylomata and fistulae are found below the stricture.



FIG 11—Twenty three and one half inch sleeve of mucosa and three condylomata stripped from Case 2 (C B)

very much like turning a coat sleeve inside out (Fig 7) With further traction sometimes the whole mucosa may be entirely removed, even through the strictured area We have, on all occasions, been able to do this in the cadaver (Fig 12) If the mucosa cannot be stripped by traction through the strictured area, then some dissection may be necessary

We next lay wide open all fistulae, and excise all of the surrounding skin condylomata (Fig 8) Formerly we removed the fistulous and condylomatous areas in a single block, but we now find, as have others,¹² that when laid wide open, all these areas will entirely heal Finally, sufficient drains are left



FIG 12—Mucosal stripping specimen from the cadaver



FIG 13—Roentgenogram of rectosigmoid in Case 1 (C S) The rectum was straight contracted and fixed in heavy scar tissue

through the dissected area from the abdominal wound to the perineal wound (Fig 9) These drains may be entirely removed in about a week The sinus thus left is irrigated twice daily with any solution desired The wounds heal more rapidly than one would expect The patient is discharged after two to three weeks, and returns to the clinic for dressings, or may be instructed to do them himself

CASE REPORTS

Case 1—C S, white, male, age 56, was admitted to the Hospital for the Ruptured and Crippled March 14, 1932 For three years he had been suffering from rectal abscesses, fistulae, stricture of the rectum, and had had several operations Examination showed an acutely ill man with a large perirectal abscess, stricture of the rectum, nine fistulous openings in an indurated ischio-rectal region, and a recto-urethral fistula through which feces and gas were passed Roentgenologically, the bowel showed a narrow fixed rectum which looked like a pipe (Fig 13) The Fier test was strongly positive An immediate incision and drainage was done of the perirectal abscess A suprapubic cystostomy cured his recto-urethral fistula We dilated the rectum and opened fistulae on several occasions

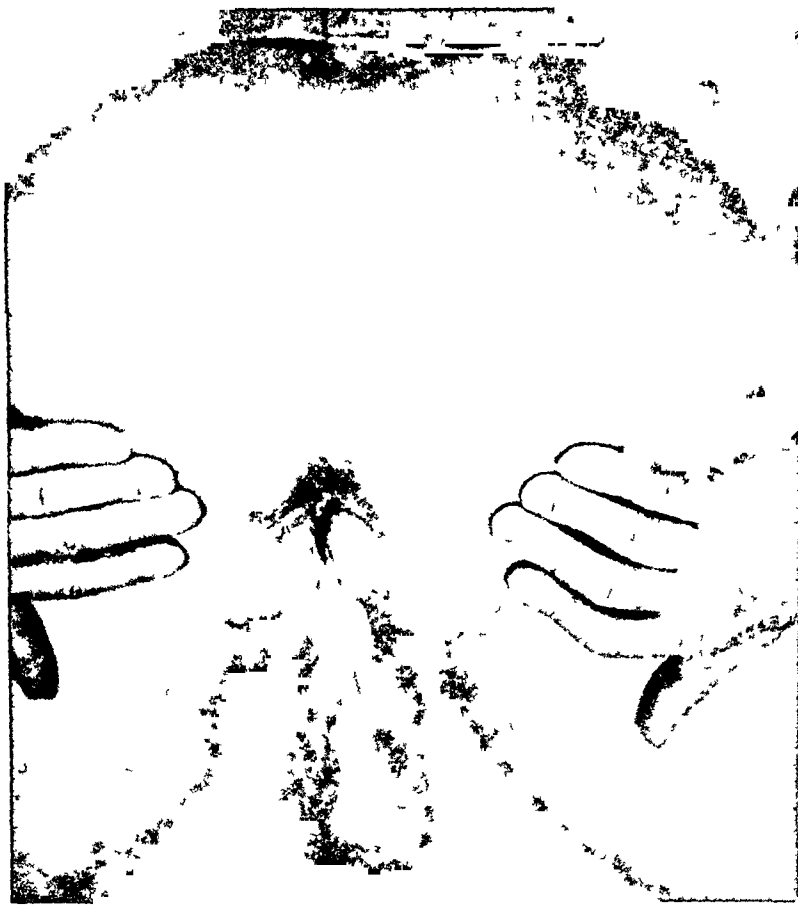


FIG 14—Anal region of Case 1 (C S), four years postoperative. Before operation he had nine fistulae, many condylomata and sinuses, and a recto urethral fistula.



FIG 15—Abdomen of Case 1 (C S), and Figure 14

during the following year. Finally, on May 27, 1933, we established a colostomy of the first-stage Lahey type. The patient improved but the mucopurulent discharge from the lower segment was a source of great inconvenience to him, and required many dressings. The extent of the disease in the rectosigmoid made the complete excision of the rectum impossible. The problem was to, at least, get rid of the mucus. On October 14, 1936, in attempting to close the lower colostomy opening, so as to have all the discharge drain



FIG 16—Abdomen of Case 2 (C. B.), operated upon 21 months previously. Clean healed scar. Wears no colostomy bag.

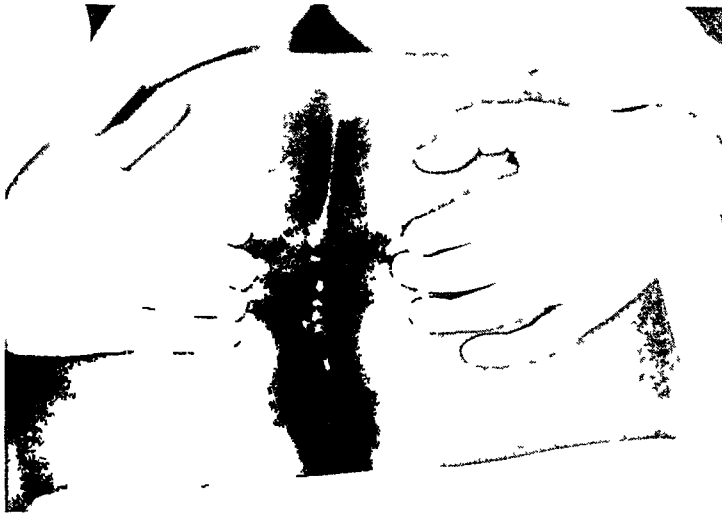


FIG 17—Anal region of Case 2 (C. B.), 21 months after the second stage operation. Before operation she had numerous condylomata, sinuses, rectal stricture, and great induration of the ischio-rectal region, with pus and bloody discharge and partial intestinal obstruction.

at the anal end, we suddenly found that, after the mucosa was freed at the skin border, we were able to pull out and strip out some nine and one-half inches of the mucosa. We then placed the patient in the lithotomy position and, by a posterior incision through the densely scarred anus, we were able to dissect out what remained of the mucous membrane and rectal wall. The patient rapidly recovered and was discharged 15 days later. The large dressings, many times a day, were reduced in three weeks to a small piece of cotton

at the anal end night and morning. The patient has trained himself so that his bowels move every morning. He has now been well for four years (Figs 14 and 15).

Case 2—C B, colored, female, age 35, was admitted to the Cornell Division at Bellevue Hospital, November 21, 1938, complaining of hemorrhoids, growth from the rectum, rectal bleeding and constipation during the previous two years. At examination we found the typical picture of a two-inch stricture of the rectum, beginning two inches inside the anus. At the anus there protruded a papillomatous growth. The whole ischio-rectal area was indurated and the seat of numerous condylomata and sinuses. Pus and blood was discharging from the rectum. The Frei test was strongly positive. On December 3, 1938, a colostomy was established and nine inches of sigmoid were removed. The condition of the patient greatly improved. On January 9, 1939, the mucosal-stripping operation was performed, 23½ inches of mucosa being removed (Fig 11). The patient was discharged 22 days later. All wounds were healed in eight weeks and have remained so to date. Her bowels move once a day. She does not wear a colostomy bag (Figs 16 and 17).

Case 3—O L, white, male, age 39, was first seen in Bellevue Hospital on December 30, 1938. He had lost 23 pounds in six months, he had rectal fistulae for 11 years, and had been operated upon at least five times in five different hospitals. Examination showed an emaciated man. The anal region was indurated, and distorted. There were nine fistulous openings, and the rectal mucous membrane was prolapsed. The Frei test was negative. On January 11, 1939, a colostomy was established and several inches of sigmoid removed. The patient's condition, generally and locally, improved. On February 28, 1939, the mucosal-stripping procedure was carried out, the entire tube of mucosa being relatively easily removed. The drain was removed in one week and the patient was allowed out of bed. In seven weeks the wounds were practically healed, the patient using a small piece of gauze at the anal end. The patient was heard of once since, and was said to be cured. We have not been able to get in touch with him further. This patient may or may not have been a case of lymphogranuloma venereum.

We have performed both stages of this operation on three other cases. The fourth and fifth cases returned to the clinic at Bellevue Hospital until they were about well. They then moved on from the Municipal Lodging House and have not returned to the clinic again.

Case 6—J A G, colored, male, age 35, had the second stage of the operation August 23, 1940. He had a strongly positive Frei test, and a venereal history extending over 11 years. On admission to Bellevue Hospital he had a partial intestinal obstruction from stricture of the rectum, multiple condylomata, and 19 rectal fistulae. After the first-stage operation, June 19, 1940, he gained 12 pounds. The rectal mucosa was stripped out August 22, 1940. The condylomata were excised and the sinuses widely incised. Drains were all removed by the fifth postoperative day, after which time his temperature remained normal. The patient was discharged, 18 days after the second operation, in good physical condition, with almost negligible discharge from the anal region. All the sinuses were clean and healing rapidly. The intestinal tube was closed above and granulating well below.

We have four other cases upon whom we have performed the first stage of the operation. One has gone through a pregnancy. We have closed her colostomy twice, and on each occasion the local condition has become worse, the colostomy was opened once by nature and once by the surgeon. The other three have, thus far, refused the second stage of the operation. They improved immediately after their colostomies but the local condition is still very active, requiring a great deal of care and dressings. Another case had his colostomy

and, even with a negative biopsy report, was found, at the second operation, to have a carcinoma of the rectum in addition to lymphogranuloma venereum. We undertook an extensive excision of the rectum but the patient died one year later with metastases of the lungs, pleurae and kidneys.

COMMENT—We have pathologic reports on all of our cases, but we have not presented them and their photomicrographs here because it is the feeling of our pathologists at Bellevue Hospital and of others¹⁸ that a diagnosis cannot be made from a tissue examination. The latter is of help in excluding other diseases, such as syphilis, tuberculosis and carcinoma. The tissue reports are always similar: Acute and chronic inflammation, submucosal fibrosis, muscular hypertrophy, dense lymphocytic infiltration, necrosis, mucosal polypi, *etc*. However, tuberculosis, syphilis and carcinoma are so frequently associated with this disease, that roentgenograms of the chest, blood Wassermann tests, the Frei test, and a biopsy should always be done. Greenblatt¹⁹ in a recent article, has drawn attention to the frequency with which genital and rectal malignancy is clothed in the guise of a venereal disease.

Because the medical profession is not yet fully aware of the inadequacy of ordinary treatment of this disease, all the authors of recent articles on the surgical treatment, have emphasized that some cases are refractory, the prognosis is bad, a systemic spread may occur, and death from sepsis, peritonitis, and cachexia happens more often than is generally recognized. A simple colostomy is a tremendous relief to these patients, and it will prolong life many years, but cases are being reported,¹² and we have seen two such cases, where the disease had extended up the sigmoid and had actually involved the colostomy stoma. We also see a few cases every year who have had a colostomy performed elsewhere and whose symptoms, locally, have increased until they are admitted to our hospital wards for further treatment. Another interesting point is the number of years a patient can go with almost complete intestinal obstruction from the stricture. We have had several cases go for three or four years with strictures through which we could not pass a small bougie. Finally, they would submit to colostomy.

The reaction after the mucosal-stripping operation is not severe. The temperature rarely rises more than two or three degrees. The patients are often anemic and need a blood transfusion. We have, thus far, only operated upon the worst type of cases with the anorectal syndrome. Out of six cases we have not had a fatality. One case with multiple fistulae and an 11-year history without a positive Frei test, was submitted to the operation and greatly benefited by it. We believe, therefore, that the operation may be indicated in certain cases of multiple fistulae, especially where the sphincter has been irreparably damaged. We offer this report as a preliminary one, and we realize that six cases are not sufficient to prove the value of the operation. We do feel, however, that the mucosal-stripping is a new idea. We would like to offer it for what it is worth. It does have the advantage of not entering the peritoneal cavity, and avoiding the consequences which may thus follow in these infected cases.

CONCLUSIONS

(1) An operative procedure for the anoectal type of lymphogranuloma venereum is described. The second stage consists of stripping the mucosa from the layers of the lower sigmoid and rectum—which we believe to be a new feature.

(2) Five cases, thus far treated, have been greatly benefited.

(3) One case of multiple rectal fistulae, not due to lymphogranuloma venereum, has been improved by this operation.

(4) We believe the operation deserves a further trial on such cases.

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DISCUSSION—DR. JOHN H. MORRIS (New York) said Lymphogranuloma inguinale has been gradually assuming a more prominent place in present-day literature and there is certainly a notable increase in the number of reported cases. Whether this increase is relative or absolute cannot be stated but it does appear probable that reclassification of rectal strictures with the consequent frequent elimination of the diagnosis of syphilis and gonorrhea may be held to account for the fact at least in some degree.

In any event, the treatment of this increasing group of cases has become a pressing problem particularly since the therapeutic approach to this disease—whether medical or surgical—has not been satisfactorily established. Reports from various sources indicate the success of conservative measures of treatment comprising the use of sulfanilamide, roentgenotherapy, diathermy, *etc.*, and there can be no doubt that many of these cases respond to such measures.

It is equally true, however, that an undetermined percentage of these cases—and particularly the type seen in the city hospitals—present a group of serious complications such as periproctitis, abscesses, strictures and fistulae. While the disease itself may respond to conservative measures, it is certain that those complications incident to it definitely demand radical surgical therapy.

It is significant that the type of surgical therapy best adapted to this condition is also not definitely established. Colostomy or colostomy plus complementary operation has been the main objective but it is to be noted that these colostomies are usually permanent and that they must be established in young patients. The ideal procedure is unquestionably that which removes a progressive lesion and restores the continuity of the intestinal tract, thus avoiding permanent colostomy. This ideal is not always attainable, however, and, therefore, the ingenious procedure described by Doctor Patterson merits consideration because of the satisfactory after-results and the unusually low mortality possibilities. In this connection it is interesting and significant to note that the progress of this disease seems to have been stayed by an attack upon the mucosa alone. There has been a general belief that the virus of this disease is spread via lymphatic channels and intramural extension. The response in Doctor Patterson's cases, if confirmed by longer observation, may well contribute valuable information to the etiology of lymphogranuloma venereum.

In view of the different types of surgical approach to this disease, Doctor Morris showed a case in which resection of the involved rectum was carried out, the intestinal canal reestablished, and a satisfactory sphincteric control accomplished.

Case Report—A Negress, age 31, was admitted to the Fourth Surgical Division of Bellevue on January 31, 1940, with a diagnosis from another hospital of acute perirectal abscess, multiple fistulae, stricture of the rectum, and a rectovaginal fistula. The Frei test was reported as positive from this other hospital.

Her illness dated back five years. The onset of the stricture began with small fecal movements that were very difficult and painful. Shortly thereafter she developed an abscess about the rectum which ruptured spontaneously. This was followed by profuse purulent discharge and fistula formation.

Five weeks before admission she consulted a physician who advised and carried out operation for the fistula. Thereafter she began to discharge pus and fecal matter from the vagina, while there was considerable bleeding from the rectum. For the succeeding four weeks she was treated by daily irrigations and packing. She was then advised that nothing further could be done for her condition.

Examination on admission revealed to the left of the anus an indurated sinus tract discharging pus profusely, and leading high up into the hollow of the sacrum. There seemed to be no discharge coming from the rectum. The entire perianal region was indurated, tender and swollen. On rectal examination an inflamed anal stricture barely admitted the tip of the index finger three inches from the anal margin.

Vaginal examination disclosed no evidence of rectovaginal fistula but an extensive, hard tender mass could be palpated through the posterior vaginal wall. Laboratory data,

2,200,000 red blood cells, 18,000 white blood cells, 92 per cent polys Blood Wassermann negative Frei test positive

During the succeeding three weeks under observation the patient ran a persistent, intermittent type of temperature with a daily maximum of 104°-106° F, and she became quite toxic The abscess about the rectum continued to drain through the vagina Vaginal examination showed the pelvis to be negative, but she continued to have the extensive perirectal mass Conservative treatment in the form of transfusions, glucose, sulfanilamide, *etc*, were carried out without demonstrable improvement In view of the progressive toxemia, it was decided that some surgical attack should be attempted

Accordingly, on February 2, 1940, a proximal short-circuit of the bowel was effected by means of a Devine colostomy at the level of the hepatic flexure The general and local condition improved markedly The patient was discharged one month after operation, with instructions for daily irrigation of the distal isolated loop

On readmission, the diagnosis of stricture was unchanged, but the discharge from the fistula had decreased, and the perirectal abscess had improved to some degree On May 11, 1940, the following procedure was carried out

A curved transverse incision was made from one ischial tuberosity to the other, with its concavity toward the rectum Dissection was carried upwards through the perineum between the rectum and vagina until the cul-de-sac of Douglas was encountered The peritoneal cavity was opened so that an uninvolved segment of bowel could be secured and the bowel was sectioned high up The distal segment was freed down to a point proximal to the external sphincter where it was again sectioned and the involved segment with stricture and thick-walled rectum removed The proximal cut-end of uninvolved bowel was then brought through the external sphincter, which had previously been denuded of its mucous membrane, after the Whitehead method, and sutured to the skin edges The wound was closed with drains in either angle of transverse wound

A satisfactory recovery was obtained, and one month after the above resection the spur of the Devine colostomy was crushed and the fecal current reestablished

In the meantime rectal dilatation had been carried out at regular intervals and the Devine stoma was subsequently closed, under local anesthesia Her present status is that colostomy wound and perineal wounds are both well healed There is no rectal stricture or fistula, no recurrence of granulomatous process, and bowel movements are normal and well controlled

This operation was originally described by Pochet, in France, and has been carried out successfully in this country by Dr Louis Wright at Harlem Hospital

DR RALPH COLP (New York) stressed the fact that lymphogranuloma venereum is becoming a real problem in the New York area because of the great increase in the Porto Rican and Negro population It is a serious, progressive, debilitating type of disease which leads to chronic invalidism, and the treatment of which should be based fundamentally upon its pathology It is probably due to a filtrable virus While it might start in the rectum as a local lesion following pederasty, this is not the usual path by which the rectum and sigmoid are involved It invariably involves the nodes of the femoral and iliac region with a cicatrization of the endopelvic fascia which results in lymph stases, producing an edema of the mucous membrane of the rectum This, abetted by the passage of the fecal content, causes a progressive ulceration of the mucous membrane with a seropurulent discharge, ending eventually in stenosis of the rectum When these lesions begin, they should be treated energetically by medical means, and some good results have been obtained from chemotherapy and the injection of the Frei antigen However, if the disease shows a tendency to progress, surgery should be resorted to As Doctor Patterson has stated, dilatation of the strictures is of little avail In Doctor Colp's experience, the results following the removal of the fibrous connective tissue about the rectum, from a posterior sacral approach, have

not been successful. Bearing the pathology in mind, the ideal procedure would be an excision of the diseased area of rectum and rectosigmoid, together with the nodes which were really responsible for the lesion. In 1925, Villard and Rickard recommended an abdomino-endo-anal resection of the rectum and rectosigmoid for carcinoma, mobilizing the sigmoid, and reimplanting it through the anal sphincters. In selected cases, this procedure, which entails a high mortality, has been employed a great deal for granuloma venereum in South America. Doctor Colp said he had employed it twice, with an excellent functional result in one case and a poor result in the other. These cases were operated upon three years ago and both are well and have had no signs of a recurrence of their disease. A more logical procedure is that advocated by Kindall and Edwards who, in 1923, advised a loop-colostomy which will divert fecal content, followed by a perineal resection of the diseased rectum and sigmoid. The reason that this procedure is a good one is that it removes the actual diseased node, and the diseased area of the bowel. Doctor Colp could not agree with Doctor Patterson that loop-colostomy *per se* may be followed by an extension of the disease in the proximal bowel. This disease probably does not spread by continuity, but the ulcerations of the mucous membrane are secondary to lymph node involvement. There are cases, however, which, because of extensive fistulization of the perineum, will not tolerate resection, and it is in this type of case that the procedure contributed by Doctor Patterson is especially indicated. The "stripping" operation rids the patient of an annoying discharge and makes his life fairly comfortable. Whether these patients will have a further extension of the disease, only time will tell. The idea is well-conceived as a palliative procedure and should certainly be tried in those cases which are truly inoperable from the standpoint of a loop-colostomy and perineal resection.

DR W HOWARD BARBER (New York) said that observations made upon the Third Division at Bellevue Hospital correspond in most respects with those of Doctor Patterson. There is a decrease in the total number of rectal lymphogranulomata admitted on the Surgical wards. This is probably due to more effective medical treatment of the constitutional aspects of lymphogranuloma venereum. A small proportion of these refractory cases continue to resist all forms of nonsurgical therapy and develop rectal stenoses and strictures, ulcerative proctocolitis, and extensive regional lymphadenitis. If these cases are not arrested by surgical means they terminate fatally by intestinal obstruction, profound toxemia and asthenia, perforation of the colon and peritonitis, or metastases and septicemia. The means of progression from the most frequent primary venereal sore is by the lymphatics to the rectal and perirectal tissues, to the regional nodes of the rectum and sigmoid, and in the extreme cases to the preaortic lymphatics and to the nodes behind the transverse mesocolon. In rare instances the virus appears to be carried by the venous blood, particularly through the superior hemorrhoidal and inferior mesenteric vessels, to the portal vein and liver. The granulomatous process may extend directly along the bowel wall but rarely above the splenic flexure, and the manner of such extension is not clear. The progression may be through the lymphatics of the bowel wall and the ulcerative colitis due to a secondary infection. In view of these observations the paramount indications for surgery are taken to be (1) Relief of intestinal obstruction, (2) ablation of the chief pathologic site of the disease, and (3) interruption of the spread of the disease within the abdomen. These are thought best met by (1) An abdominal colostomy, and (2) sacroperineal resection of the rectosigmoid together with the involved pararectal and presacral lymphatics. The

results of this program in our wards have been followed by a striking improvement in the weight and well-being of the cases operated upon and a mortality of 14.3 per cent for the first 35 resections.

Doctor Patterson has presented a very interesting thesis on the stripping of the mucosa from the rectosigmoid and resection of the anorectum, following a preliminary abdominal colostomy. This is applicable in those cases wherein the mucosal lining is not too involved to be separated from the remaining rectal wall and above the stricture. Excision of the remaining stenosed rectum and anus eliminates a considerable portion of the most diseased tissues.

Doctor Morris' case of rectal resection with preservation of the anal sphincter for control of a perineal colostomy has been well executed by him. Such procedures have been reported by Colp and others with varying success. Our experiences with anal plastics have led us to avoid them. In the interest of more complete eradication of the diseased bowel we prefer to produce sacral colostomies where it is possible or desirable.

DR RUSSEL H. PATTERSON (New York) said, in conclusion, that the patient had had his colostomy in 1932. The mucosal-stripping operation was performed in 1934. It has now been six years and the patient has gained 30 pounds in weight and is up and about at his business every day. One case shown tonight had the mucosal-stripping procedure carried out only a few weeks ago. The case was presented to demonstrate how the healing process takes place. The second patient had the mucosal-stripping procedure carried out one year ago. She has had no symptoms or signs of a recurrence of her trouble.

In response to Doctor Colp's mention of the mode of acquisition of the anorectal type of this disease, Doctor Patterson said he had purposely avoided this controversial phase of the subject. There are two main schools of thought as to mode of acquisition. One school believes that the virus comes in contact with the mucous membranes of the genitalia and spreads to the inguinal nodes and eventually to the pelvic nodes and the perinectal tissues. The other school believes that the virus is deposited directly on the rectal mucous membrane, as the result of pederasty, an acute proctitis results, and eventually a stricture of the rectum. Doctor Patterson said he leaned toward the belief of the latter school. Doctor Arthur Grace of the New York Hospital, in examining some 200 cases, obtained a positive history of pederasty from 80 per cent of the male patients.

Doctor Patterson expressed the opinion that the procedure described by Doctor Morris in the case he showed is excellent for rectal strictures that are uncomplicated by sinuses and infection. Doctor Patterson said he had been encouraged in the one case upon whom he had operated in a similar way. Simple colostomy does help a great many of these patients. However, Doctor Patterson felt more radical surgery is needed in the severe cases such as those described in his paper.

ENDOMETRIOSIS—ITS SIGNIFICANCE¹

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IN AUGUST, 1938, in an editorial,³ attention was drawn to the fact that endometriosis was increasing in frequency and that there was probably some reason for it. It was felt that the increase might be due to delayed marriages and to lack of early and frequent child-bearing, and suggested that the economic difficulties of the day were responsible for the increased frequency.

Since that writing, all cases in my private practice have been very carefully explored, and any piece of tissue suggestive of endometriosis has been excised and fixed in Zenker's solution before the removal of any organ was begun. Probably, the fact that pieces of tissue have been separately removed and preserved, is partly responsible for the finding of increased numbers of this lesion. It is also probable that because of the great increase in total hysterectomies, with a wide exposure of the posterior cul-de-sac and the uterosacral ligaments, more small posterior lesions have been found. The high percentage of positive microscopic findings and the greater percentage of gross findings have led to the conclusion that endometriosis is brought about by a physiologic response to persistent and uninterrupted menstruation. Something (estrin?) stimulates the celomic epithelium and this stimulation causes the epithelium to attempt to produce small areas of endometrial tissue, endosalpingial tissue, or even endocervical tissue. So great is the concern about this lesion and its frequency, with its definite lowering of fertility, that patients with stigma of lowered fertility are urged to marry and bear children early. Normal girls over 23 are urged to have a child as soon as possible after marriage. Many men and women cannot afford to be burdened with children immediately after marriage, but as youth is the proper time to have children it is right that they be urged to do so. Dr. Thomas R. Goethals, of Boston, found that in 75 per cent of 200 private primiparae the average age at the birth of the first child was 28 years. All this fits into the theory that an apparent increase in this entity is due to the economic difficulties of our times. Sampson,⁷ in 1924, reported 64 instances in 296 celiotomies, or 21.6 per cent, and, in 1925,⁸ 98 out of 332, or 29.5 per cent—a total of 162 out of 628, or 25.7 per cent. These statistics of Doctor Sampson are high, but it must be remembered that at that time, because of his work with endometriosis, patients from everywhere, who were suspected of having the disease, were being sent to him. This, I believe, has something to do with the figures presented. The cases described in this article were sent because of varied pelvic pathology, and none were suspected of having endometriosis.

* Read before the American Surgical Association, White Sulphur Springs, W. Va., April 28-30, 1941.

Definition—There are two main types of ectopic endometrium. In one, and this does not figure in this communication, the endometrium is found growing down from the endometrium into the myometrium. It may invade the myometrium very deeply, but usually is made up of a few glands growing away from the normal lining of the uterus, occasionally the growth penetrates the entire uterus, and may even invade incidental fibroids that are present. This lesion is known as adenomyoma or adenomyosis.

The second type, and the one that is being discussed here, is made up of areas of ectopic endometrium, either in the ovary, tube, pelvic peritoneum, on the front of the uterus, or in the uterosacral ligament, *etc.* The lesion may be widespread and the whole pelvis bound down by adhesions, or there may be a spot no larger than the head of a pin. The area may be blue, black, or purple, or there may simply be a pucker in the otherwise smooth pelvic peritoneum. Sections of this tissue will show glands similar to endometrial glands and a stroma similar to endometrial stroma. This tissue may respond to the stimulation of estrogen to produce the growth phase, or to progesterin to produce the secretory phase, or to pregnancy to produce decidua in the stroma, but just as the basal layer of the normal endometrium does not react to any ovarian stimulus, so also this tumor may not. However, enough cases have been seen that respond to ovarian stimulation, and that are so very like endometrium in microscopic appearance, that it is fair to assume that they are one and the same thing. I doubt if anyone questions, now, that the endometrium of endometriosis is not similar to normal uterine endometrium.

Theories for Development—Cullen,¹ long ago, showed that the first type of endometrioma, the adenomyoma, is a down-growth from the endometrium, and that the glands are often connected with the endometrium. In a series published² from the Massachusetts General Hospital, in 1934, it was definitely shown that this lesion was more frequently present in women who had had multiple pregnancies. This is due, perhaps, to the growth and involution of the uterus and the activity of the endometrium as it passes through numerous pregnancies. Perhaps small pieces of tissue are caught in the myometrium when the changes take place.

Sampson postulated the idea that endometriosis is due to two possibilities. One, that the endometrium during a normal menstrual period may be swept in a backward direction and flow into the peritoneal cavity and attach itself and grow upon or into any pelvic organ, two, that an ovarian endometrioma may menstruate, swell, and rupture, and in rupturing spread endometrium that is viable into the pelvis, or itself become attached to the peritoneum and grow and invade it. This study cannot refute this theory, nor does it attempt to do so. In nearly every one of our cases the tubes were patent—a proof that reflux could take place. All of us have seen reflux bleeding during a period. The many years of uninterrupted menstruation in these cases would seem to give greater chances for the endometrium to flow through and grow. If, however, the menstrual flow is due to sloughing off of tissue that has become anoxic (a current theory of menstruation) I think that it is unlikely that the tissue

that comes through the tube would be viable. Nature certainly did not intend that reflux bleeding should be responsible for the growth of invasive tissue in the pelvis. Menstruation itself may be a kind of abnormality, for it occurs only infrequently in monkeys in their natural habitat.

The theory of lymphatic extension, that is metastasis of endometrium through the lymphatics, probably is not the correct method of its spread. However, many very able men believe in this theory.

Iwanoff and Meyer⁴ have proposed that inasmuch as the pelvic peritoneum is the celomic epithelium, and as the celomic epithelium is the original source of the endocervix, endosalpinx and endometrium, this tissue may still contain groups of viable embryonic cells, and under certain conditions they may grow, and in growing reproduce what they produced in the embryo. It is thus possible that just as the endometrium and endosalpinx and endocervix respond to estrin and progesterin by growth and function the pelvic peritoneum (celomic epithelium) may grow and produce if the stimulation is constant and not interrupted, as it should be, by pregnancy. Interruption of the menstrual cycle by pregnancy is a physiologic change in women. When it is realized that the frequency of endometriosis in patients with stigma of underdevelopment is twice as great as in those without it, this theory is even more tenable, for patients with underdevelopment may have more left-over cells. If pregnancy is a check upon the development of endometriosis, and I believe it is, what is there in pregnant women that checks the celomic epithelium from growing? Certainly estrin and progesterin are produced in greater quantities during the pregnant than in the nonpregnant state. This normal physiologic process, although perhaps not preventing it, must have something to do with avoiding endometriosis. It is probable that this theory is the correct one, namely, that epithelium which originally grew endometrium can, under certain abnormal conditions, again produce cells capable of becoming endometrial tissue.

Symptoms, Diagnosis, and Treatment—These have been described so many times that this paragraph will be brief. The symptom occurring most frequently is that of acquired dysmenorrhea, which is usually accompanied by a change (increase in the amount) of the menstrual flow. The physical diagnosis is not difficult in a patient over 29 years of age, who presents symptoms of pelvic inflammation, who has had no children, and who, on vaginal or rectal examination has a moderately fixed pelvis with a rough or shotty feeling in the posterior cul-de-sac. Such findings may be interpreted as the result of endometriosis. The treatment may be radical or conservative, depending upon the age of the patient, the extent of the disease and the patient's desire for children. Occasionally, bilateral oophorectomy will be necessary. Roentgen therapy destroys ovarian function, and this is followed by atrophy of the endometriosis as well as atrophy of the normal endometrium. Therefore, one can be conservative when it is deemed best. In older women, radical surgery is best if it can be undertaken without danger to the life of the patient. This tumor can be very difficult to remove, and injury to the rectum, bladder, uterus, or intestines can occur. At operation, it is frequently noticed that the uterus is flexed backward upon itself, the fundus and cervix being

attached to one another, the uterosacral ligaments are obliterated, and the posterior cul-de-sac drawn up on back of the bent uterus. This must be recognized during operation as perforations of the rectum or incomplete surgery may otherwise result. When the uterus is straightened out and the cul-de-sac freed, a very wide, raw area will be found on the posterior wall of the uterus and in the cul-de-sac of Douglas. This is definite evidence of abnormal development and endometriosis is often recovered from these areas. The uterosacral ligaments may be missing following release of the uterus and cul-de-sac.

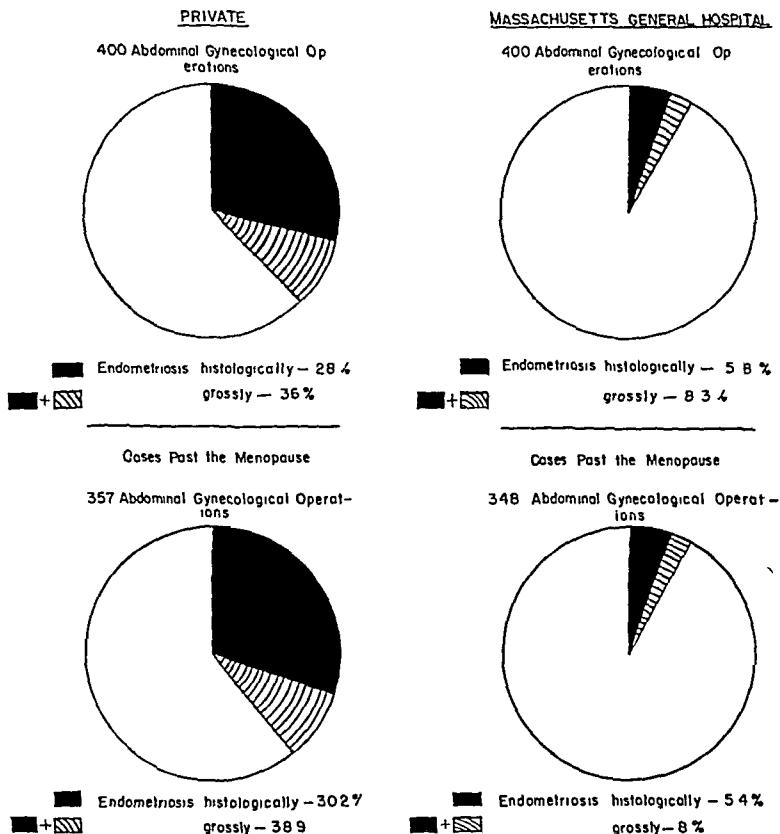
Increased Frequency—The increased frequency may be actual, or it may be due to more careful observation and better exposure of the cul-de-sac and uterosacral ligaments. But there is probably more to it than that, for during my apprenticeship with the late Drs. W. P. Graves and G. W. W. Brewster, from 1921 to 1927, search was made for these lesions because of the great interest aroused by Doctor Sampson's observations. Yet not a great number of lesions were found. That is probably because the patients operated upon, then, were married earlier and bore children earlier than those who have been operated upon during the last four to five years. It is probably true that our mothers and grandmothers married early and had many children, and that they rarely had this abnormal physiologic process. There is no doubt that great interest stimulates more careful search. The habit of placing sutures about the areas, or placing safety-pins under them, or even excising the areas has been developed. In the early cases in this group, numerous areas of endometriosis were missed in the laboratory, for a blood-covered uterus is not the easiest place to find the fine, blue to purplish spots that represent this growth. Doctor Tracy B. Malloy, the Pathologist at the Massachusetts General Hospital, has admitted that my diagnosis, in the gross, is probably as correct as his by microscope, and if that is so, then the number is even greater than the histologic findings would indicate. I have been a student of this lesion since Doctor Sampson first drew attention to it, and I have worked and puzzled about it for years.

I believe that the theory of Iwanoff and Meyer is the correct one and that the great frequency of endometriosis, as reported in this communication, is due to careful observation and the removal of pieces of tissue, but that the real reason for the frequency is that endometriomata are not tumors but represent abnormal physiology due to late marriage and delayed and infrequent child-bearing. The latter is due to the economic times we live in, and my plea is that patients with apparent infertility, evidences of underdevelopment, and older girls about to be married, be taught how to become pregnant and not how to avoid pregnancy even though their finances are limited. The monkey mates as soon as she becomes of age, and has offspring until she can no longer have any or until she dies. Menstruation in this animal must be rare. As women have the same physiology it must be wrong to put off child-bearing until 14 to 20 years of menstrual life have passed. During a prolonged, uninterrupted menstrual career changes in the celomic epithelium from whence the endo-

metrium originally came must take place Endometriomata are not true tumors but are areas of growth due to abnormal physiology Another important finding is the comparison of private patients, most of them fairly well-to-do, to a similar group of patients at the Massachusetts General Hospital The hospital patients are of that social status that marries early and has children frequently, and in this group there are fewer cases of endometriosis Their more normal functions are reflected in the small incidence of endometriosis

TABLE I

	Private	M G H
Abdominal gynecologic operations	400	400
Histologic endometriosis	112-28%	23-5.8%
Gross endometriosis	144-36%	33-8.3%
Abdominal gynecologic operations Excluding cases past the menopause	357	348
Histologic endometriosis	108-30.2%	19-5.4%
Gross endometriosis	139-38.9%	28-8%



Diagrammatic representation of Table I

The Material—The last 400 consecutive abdominal gynecologic operations in my private practice were analyzed very carefully, and certain important findings noted. Four hundred consecutive patients who had had abdominal gynecologic operations at the Massachusetts General Hospital were studied to find the percentage of endometriosis to compare with the private group. In

the group of patients who came to my office, and were operated upon by me, 112, or 28 per cent, showed microscopic evidence of endometriosis, as against 58 per cent in the Massachusetts General Hospital group. The number of patients who were considered, grossly, to have endometriosis at operation was 144, or 36 per cent (Table I).

These patients were not, in many instances, suspected of having endometriosis before operation, and in many instances the endometrioma consisted of a very small isolated area. The point is, however, that they had what we understand as endometriosis, and it might easily have grown larger if let alone. The process was there, though not giving any symptoms.

A comparison was then made between the endometriosis group and the rest of the 400 who did not have endometriosis. In the endometriosis group, 74.1 per cent were married, and of the others, 74.3 per cent were married. In the endometriosis group, 53.1 per cent were over 25 when married, and in the other group, 57.3 per cent. These statistics are, so far, all nearly identical. But the fertility in the endometriosis group was 65.7 per cent, while in the other group it was 83.3 per cent (Table II). This latter figure for fertility is

TABLE II
400 ABDOMINAL GYNECOLOGIC OPERATIONS (PRIVATE)

	Endometriosis	No Endometriosis
Married	74.1%	74.3%
25 years of age or over at marriage	53.1%	57.3%
Two children or less	73.4%	49.3%
Fertility of married group	65.7%	83.3%
Stigma of underdevelopment	27.6%	15%
Marriage to first pregnancy over two years	69%	66.6%
Age at first pregnancy 25 or over	63.4%	
Age at onset of symptoms over 27 years	108 cases	
Menarche to endometriosis 17 or more years	105 cases	
Number of years from menarche to first pregnancy		
11 or more years	73%	
Age of patients with endometriosis over 29 years	All but one	

too low, but this is not unexpected, as most of the patients were operated upon for fibroids, cancer, bleeding, ovarian tumors, *etc*, so that they also must have a lowered fertility. Reynolds and Macomber⁵ in their book on Fertility and Sterility, give 88 per cent as normal fertility in the married. Congenital erosions (exposure of the endocervix), very painful breasts, narrow pelvis, severe dysmenorrhea, juvenile uterus (measured), and infrequent periods were considered as stigma of underdevelopment. The endometriosis group had 27.6 per cent of patients with evidences of underdevelopment, while in the other group there were but 15 per cent. The endometriosis group, therefore, showed nearly twice as many patients with underdevelopment. Seventy-three and four-tenths per cent of the patients with endometriosis had two or less children, whereas in the other group 50.7 per cent had over two children. Sixty-nine per cent of the endometriosis group did not have the first child until two or more years after marriage, and of the other group 66.6 per cent did not. Other statistics of interest are as follows. For the group with endometriosis, the age at the first pregnancy was 25 or over in over 63.4 per cent, the age of the onset of symptoms was over 27 in 108 of 112 patients. The age of patients

with endometriosis, when it was found, was over 29, in all but one patient. The number of years from the onset of periods to the finding of endometriosis was 17 years or more in 105 out of 112 patients. In 57.4 per cent of the endometriosis group there was a change in the patient's characteristic menstrual flow. The preoperative diagnosis was made correctly in 41 per cent of patients. Endometriosis was found in the ovary in 57.1 per cent, on the peritoneal surface in 51.6 per cent, and in 18.7 per cent its location was the uterosacral ligament. In 32.1 per cent of patients dysmenorrhea was a complaint, 33 per cent complained of pain other than dysmenorrhea, 23 per cent had urinary difficulty, and 28.6 per cent had bowel habit changes. There were 85.7 per cent who had a radical operation, that is hysterectomy with or without removal of the ovaries, and but 14.3 per cent had conservative surgery. Three patients with conservative surgery had children following operation (Table III).

TABLE III

Region of Endometriosis	
Ovary	57.1%
Peritoneum	51.6%
Uterosacral ligament	18.7%
Operation	
Radical	85.7%
Conservative	14.3%
Symptoms	
Dysmenorrhea	32.1%
Pain other than dysmenorrhea	33%
Urinary symptoms	23.2%
Change in catamenia	57.4%
Bowel symptoms	28.6%

CONCLUSIONS

(1) Delayed marriage, delayed and infrequent child-bearing all contribute to an increase noted in endometriosis.

(2) Less well-to-do patients in a general hospital population have less endometriosis than patients in private practice.

(3) Stigma of underdevelopment means lowered fertility and greater incidence of endometriosis.

(4) The celomic epithelium or pelvic peritoneum may be stimulated to produce endometriosis (Iwanoff and Meyer).

(5) Modern economic trends are responsible for delayed marriage.

(6) Young married couples should be urged to have children early, and practice contraception after they have their families. They should be taught how to have children, not to avoid them.

(7) Financial aid from parents in the early years of marriage should be offered and welcomed when possible.

The significance of endometriosis is that it is a stigma of infertility, and it is due to uninterrupted menstrual cycles, because of late marriage and infrequent child-bearing. Therefore, as it is increasing in private practice among those having children late in life and few in number, it is better for us, as doctors and fathers, to urge early marriage and early and frequent child-bearing.

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DISCUSSION—DR JAMES C MASSON (Rochester, Minn) Doctor Meigs' paper is on one of the subjects that are foremost in the minds of gynecologists at present, and there is no doubt that those who are "endometriosis-minded" find this condition frequently, whereas the general surgeons, and those who are not especially interested in the subject, see it rather rarely I was impressed by the carefully prepared and convincing statistics of the essayist There is no doubt that the condition is recognized more frequently than formerly, and the reason for this is probably that a real interest in the subject was stimulated by Sampson's paper about 20 years ago Since that time, operations have become more frequent, especially more radical operations including total hysterectomy, and the more frequent examination of tissue removed has been, as suggested by Doctor Meigs, a factor in the more frequent recognition of the condition

The possibility of delayed marriage, and of delayed child-bearing, has to be considered, but in this connection I would like to note that 50 per cent of the patients in my series were married before they were 24 years of age I am sorry that I cannot give the dates when their first babies were born In one case, endometriosis was diagnosed one year after the onset of the menstrual periods

In one case, I reported to this Society in 1935, when I presented a paper on this subject, the patient had rather extensive endometriosis in which the only serious lesion, I feel, was the one on the sigmoid It was a benign tumor, but might grow sufficiently to cause obstruction Another very important condition in this case was an adenomyoma in the rectovaginal septum The "endometriosis-minded" surgeon frequently sees small implants in the cul-de-sac, on an ovary, or on the uterosacral ligaments Many of them, I think, never cause serious trouble and, unless the tubes are occluded, pregnancy is still possible

It is my impression that a great many of the smaller endometrial implants suggest, very strongly, Sampson's idea of a reversal of the flow of the menstrual fluid I think a great many of them eventually disappear I want you to keep in mind this picture, and I will refer later to large, tarry cysts and endometrial tumors in ectopic positions

I want to draw attention to the number of cases in which endometriosis was located in the uterus in my series In 482 of 576 cases encountered, the adenomyomata were in the uterus A great many of these were diffuse adenomyosis of the uterus, but there were numerous implants on the visceral peritoneum In 14 cases, endometrial implants were on the sigmoid, in 20 cases, in the rectovaginal septum and in 77 cases, in the ovary Some were huge, tarry cysts In recent statistics, the number of large tumors or cysts remain about the same but there is a great increase in the smaller implants

If persistent and uninterrupted menstrual periods have a marked influence on this condition, then I would think that a younger married woman would have to have many children to protect her until the time of her menopause If she had two, three, or four children early, and then started contraceptive methods, she would have a long period of

constant and uninterrupted menstrual periods and, if Doctor Meigs' theory is correct, endometriosis might develop later in life

Doctor Meigs has made a strong case for the hormonal influence of estrin on the columnar epithelium, as suggested by Meyer. In 1935, in speaking on this subject before this Society, I expressed the opinion that many of the tumors which are similar, microscopically, may have different origins, and I still believe it. Besides the stimulation of the columnar epithelium, I think the possibility of embryonic rests being stimulated in the same way and the occasional possibility of blood or lymph stream metastasis must be admitted. I have seen cases of endometriosis in the abdominal wall, and one case of endometriosis in the lung, and one instance of endometriosis in an arm have been reported. I think lesions of this type, which are microscopically similar to endometrium, could only reach such sites by way of the blood or lymph stream.

Doctor Sampson's theory seems reasonable and possible, especially in these multiple, small lesions which are scattered through the pelvis. I think it accounts for many of the ovarian implantations. It seems possible that the ovary is very susceptible, especially in an area where there is recent corpus luteum, and that an endometrial cell, becoming implanted there, will grow rapidly and produce tarry cysts. The tarry cyst ruptures and spreads endometrial tissue throughout the pelvis. Cullen's theory of direct extension is also possible in many cases.

I believe many smaller areas never grow, and probably are destroyed or absorbed by the peritoneum.

Doctor Meigs referred to underdevelopment. I have not paid attention to the etilogic factor he mentioned, as much as I should, but in cases of congenital anomalies of the pelvic organs, including absence of the uterus, with normal ovaries and normal internal secretion, I have not seen a case of endometriosis, in spite of the fact that some of these patients have been married several years.

Doctor Meigs has covered the diagnosis and symptoms, and there is no doubt that "endometriosis-minded" surgeons make a preoperative diagnosis in a large number of cases, and, at operation, suspected tissues are removed and examined more routinely by competent pathologists.

None of us, including Doctor Meigs, recognized many cases 20 years ago, but Doctor Sampson, in Albany, was finding endometriosis in more than 20 per cent of the cases in which he performed abdominal or pelvic operations as long ago as that. As Doctor Meigs suggested, it is possible he was seeing selected cases, but the incidence of endometriosis in his cases seems large compared to the incidence in most of our cases. Many of us, I am sure, do not remove or record many pin-head-size areas of discolored peritoneum when operating for some other major pathologic condition.

Among younger women, when it seems advisable to perform conservative operations, I believe it is advisable to cut the presacral nerve at the time of pelvic surgery in order to relieve dysmenorrhea, which is often a major complaint.

No group of benign gynecologic conditions causes me more concern than advanced and extensive endometriosis among young women. In recent years, I have been more conservative than formerly, especially with the use of roentgen or radium irradiation. Now, I believe, the patient's best interests are being served by saving some ovarian tissue, in spite of the risk that a second operation may have to be performed or menopausal dose of radium or roentgen irradiation administered at a later date.

DR JOE VINCENT MEIGS (Boston, Mass. closing) I would like to add just one or two things. Not all cysts with chocolate fluid in them are endometriomata. The diagnosis must be made histologically before it can be accepted, and a great many of these cysts are not true endometriomata.

If children are born when a patient is young, and there is, thereafter, a long uninterrupted series of periods, fibroids are likely to occur as well as other benign pelvic growths. I do not think there is any question about it.

The percentage of endometriosis will increase in relation to the number of small suspected areas that are removed before the surgery begins, and put in solution for the pathologist to examine.

The most important deduction from the paper is that, if 36 per cent of 400 patients have endometriosis, it must indicate that endometriomata are not true tumors at all. They must represent abnormal physiology.

INTRA-ABDOMINAL HERNIA—REVIEW OF 39 CASES IN WHICH TREATMENT WAS SURGICAL

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THE INCIDENCE of intra-abdominal hernia, treated surgically, is extremely low, as is shown by the fact that from 1910 to 1939, inclusive, only 39 instances of such a condition have been encountered at the Mayo Clinic. The occurrence of this condition, although rare, is much greater than this figure would suggest, for the majority of intra-abdominal herniae exist without producing symptoms and are discovered only at postmortem examination. Inasmuch as an intra-abdominal hernia may be an asymptomatic complication which is found incidentally during an operation for some other condition or which may be found to be the causative factor of some type of intestinal obstruction or the exciting influence for vague abdominal distress, pain or tumor, a review of our cases seemed justifiable.

Herniae that protrude, not through defects in the walls of the abdomen, but into an abdominal pouch or opening of the peritoneum, may be considered to be "intra-abdominal" or "internal herniae." These may be primary, a direct result of some congenital defect, secondary or postoperative sequelae, or referable to trauma or inflammation not the result of an operation. Thus, they include (1) Those which occur in normal pockets, such as the foramen of Winslow, paraduodenal, paracecal, and intersigmoidal fossae, (2) those occurring in exaggerations of normal mesenteric folds, such as those in the broad ligament, (3) those resulting from traumatic or operative bands or adhesions, (4) those resulting from chronic inflammation, and (5) those which occur in anatomic defects.

A classification of internal herniae is difficult, but for the benefit of organization and presentation we have divided our cases into four groups: (1) Postoperative, 19, (2) paraduodenal, eight, (3) malformations, eight, (4) miscellaneous, four. Each group will be subdivided and discussed in some detail.

General Considerations—In general, of the 39 cases, 21 (54 per cent) have been considered to be secondary, and 18 (46 per cent) primary. In 20 instances the hernia developed secondarily, previous to performance of some surgical procedure.

The symptoms presented by the herniae were, for the most part, varying degrees of intestinal obstruction. In 29 cases (74 per cent) the hernia was considered to be producing symptoms, and in 10 cases (25 per cent) no symptoms were caused. In the 10 cases in this latter group the hernia was an incidental observation at the time of operation for some other condition. The symptoms, for the most part, were vague and not characteristic. A preoperative diagnosis seldom was made. Some degree of obstruction of the small intestine was present in 28 (71 per cent) of the cases. In 19 cases (48 per cent) the onset was marked with acute obstruction of the small intestine. When obstruction was not present, pain or the presence of a tumor was the factor which prompted surgical intervention. In every case reviewed, operation was performed.

Postoperative Hernia—Intra-abdominal hernia, as a postoperative complication, may be immediate or delayed. As a result of several factors potential internal herniae are likely to afflict patients following performance of a surgical procedure. Failure of the transverse mesocolon to remain attached to the stomach following posterior gastro-enterostomy may result in an aperture through which a loop of small intestine may slip into the lesser peritoneal sac and cause obstruction. Adhesive bands resulting from inflammation can form the opening through which the bowel may herniate. These occur more commonly following various pelvic operations and secondary to operations for ruptured appendix. Twenty such cases are included in our series.

Herniation of the small intestine through the transverse portion of the mesocolon into the lesser peritoneal cavity evidently was an occasional occurrence early in the history of gastro-enterostomy. Hernia of the small intestine through a congenital opening in the transverse part of the mesocolon has been reported, but is exceptionally rare. When this condition occurs it can be recognized easily at operation and presents little difficulty in treatment. When a hernia is found in the lesser peritoneal cavity and the foramen of Winslow is patent, an opening should be looked for in the transverse part of the mesocolon. Since surgeons, appreciating the risks involved, have been increasingly careful to close the edges of the openings in the transverse part of the mesocolon around the stomach and jejunum, herniation into the lesser peritoneal sac has become infrequent. Although the majority of internal herniae occurring secondarily to gastro-enterostomy have occurred because a portion of the small intestine slipped through the artificial opening in the transverse part of the mesocolon, a few other types of herniation have occurred. In these few, the intestine slipped behind the loop of jejunum which is formed by every anastomosis, whether it is antecolic or retrocolic. After performance of posterior gastro-enterostomy, the proximal loop of jejunum is attached at two points, namely, the duodenojejunal junction, and the stoma. This forms an artificial foramen bounded posteriorly by the peritoneum over the vertebral column, superiorly by the transverse part of the mesocolon and stomach, and anteriorly and inferiorly by the jejunum.

This foramen can be avoided by shortening the proximal loop employed in performing gastro-enterostomy and by suturing the margins of the opening together, utilizing the jejunum and transverse portion of the mesocolon. In spite of the fact that these various openings are closed at the time of operation, herniae have developed in a certain number of patients. This occurrence may be referable to some error in technic in the closure, or to inflammation, rapid absorption of the suture material used, or subsequent trauma.

There were ten cases in this series in which an internal hernia developed secondary to performance of gastro-enterostomy. In eight instances, posterior gastro-enterostomy, and in two, anterior gastro-enterostomy, had been performed. In six instances, the hernia occurred through the transverse part of the mesocolon. The bowel was herniated behind the proximal limb of jejunum in the retrocolic position in two instances, and in the remaining two, it was herniated behind the jejunum in its antecolic position. In two cases, the symptoms necessitated surgical treatment within one week after performance of gastro-enterostomy, whereas in the remaining eight cases a period of from three to eight years had elapsed from the time of performance of gastro-enterostomy to the secondary operation. In three instances, the symptoms were classed as "acute intestinal obstruction" and in seven cases, the symptoms were intermittent, vague, and of a chronic nature. Of the seven cases in which the patients were not operated upon for acute symptoms, a gastrojejunal ulcer had been suspected before the operation, but in only three instances was a gastrojejunal ulcer actually present. The hernia produced symptoms in nine cases, in three, acute intestinal obstruction, and in six, varying degrees of intestinal obstruction. The symptoms in the tenth case were attributed to gastrojejunal ulcer and the hernia was considered to be an incidental finding. Although roentgenographic examinations were made in every instance, and although the possibility of a mechanical defect was suspected, the preoperative diagnosis of herniation was not made in any case.

It is probable that in some cases intra-abdominal hernia develops following performance of gastro-enterostomy for peptic ulcer but the hernia goes unrecognized. Other herniae have been reported to afflict patients following resection of the stomach with anastomosis to the jejunum. The presence of this type of hernia is difficult to recognize, but in those cases in which gastrojejunostomy has been performed and symptoms of intestinal obstruction develop, or in which some mechanical defect in the anastomosis is present, the possibility of herniation must be considered. Such herniae can be prevented for the most part by accurate closure of all openings in the transverse part of the mesocolon and by obliteration of the gastrojejunal hiatus. The following case is typical.

Case 1—A woman, age 24, had undergone posterior gastro-enterostomy in 1936 for duodenal ulcer. Six months after the operation, distress developed which was different

from that which had been present prior to operation. About one hour after the eating of a heavy meal, she became "bloated," experienced mild cramp-like sensations in the midepigastrium, and a sense of pressure beneath the xiphoid process. One evening she was awakened by severe, intermittent colicky pain in the epigastrium, this was associated with persistent nausea and frequent vomiting of bile-tinged vomitus. The pain gradually localized in the left side of the abdomen, and operation for acute intestinal obstruction was advised. At operation, the entire small bowel was found to be obstructed and protruding through a small opening in the transverse portion of the mesocolon just adjacent to the site of anastomosis. This hernia was reduced and the opening was closed. The patient has remained free of symptoms since.

Occasionally, the intestinal obstruction has occurred secondarily to an intra-abdominal hernia caused by the formation of an aperture lateral to the loop of colon brought out during colostomy. Two such cases are included in our series. A typical case has been reported by C. H. Mayo and Magoun.⁵

Although the previously mentioned type of hernia occurs infrequently, every precaution should be taken to avoid it. This can be done by carefully and securely closing with sutures the mesosigmoid to the left parietal peritoneum. The finger should be inserted to demonstrate that all openings which might be potential causes of hernia have been closed.

Following an operation for retroversion, some error in technic may occasionally be the cause of formation of a potential internal hernia. This type of hernia has occurred most frequently following performance of the Baldy-Webster type of operation, during which the suturing of the broad ligament to the round ligament at the points of perforation of the broad ligaments was either overlooked, or after which the suturing has secondarily broken down. On the other hand, the round ligaments may be drawn through the broad ligaments too far away from the body of the uterus, so that, secondarily, a strain on these ligaments may cause the round ligaments to cut through the broad ligaments toward the median line, thus producing an aperture through which herniation of small intestine may occur.

Occasionally, in patients for whom no previous surgical treatment has been instituted, pouches and openings in the broad ligaments have been observed. These, for the most part, are considered to be congenital in origin, but in certain cases it is possible that distention and stretching arising from pregnancy, from a large pelvic tumor, or from a pelvic inflammatory disease may have produced them.

In other instances, in performing such operations as myomectomy, oophorectomy, appendectomy, and the like, openings are inadvertently made in the broad ligaments. These may go unobserved and become potential causes of herniae. In the performance of other pelvic operations in which the uterus is suspended, instances of herniation of intestine between the uterus and anterior abdominal wall have been reported.

Three patients in our series had hernia of the broad ligaments. In two cases these herniae followed performance of the Baldy-Webster type of operation for retroversion. In each of these cases, an acute intestinal obstruction was present, whereas in the case in which the hernia was of con-

genital origin, the tube and ovary had herniated themselves into a pouch in the right broad ligament and were producing symptoms. The following case is typical.

Case 2—A woman, age 47, had undergone a Baldy-Webster type of operation 16 years before admission to the Mayo Clinic. Thirteen years before her admission to the Clinic she had an internal shortening operation. On her admission a diagnosis of obstruction of the small intestine was made. At operation, two loops of strangulated ileum were found to have herniated through the right broad ligament. The hernial opening was situated just below the utero-ovarian ligament, where the round ligament had been pulled through a perforation in the broad ligament.

Herniation of this type can be prevented if all points of perforation in the broad ligaments are closed at the time of operation. In performing such operations as ventral fixation, Gillian suspension and the like, the surgeon should be careful to leave no aperture through which herniation may occur. This condition can be suspected when the symptoms of acute intestinal obstruction occur in a patient following performance of operative suspension for fixation of the uterus.

In five patients in our series, acute intestinal obstruction developed subsequent to the formation of intra-abdominal hernia as a result of previous surgical treatment. In each of these cases, there was a history of infection or peritonitis following the previous operation. Herniae of this type may develop during immediate postoperative convalescence, but as a rule are discovered a number of months or even years later, when the patient is admitted for an acute intestinal obstruction. In the five cases, the obstruction developed 4 and 6 weeks, and 8, 14, and 16 years following performance of the original operation. In three instances, the herniae were secondary to operations for ruptured appendices, and in the other two instances, pelvic operations had been performed.

Case 3—A woman, age 43, had undergone a suspension operation for fixation of the uterus and also appendectomy in 1924, and, in 1936, abdominal hysterectomy had been performed. One month following this operation, acute obstruction of the small intestine developed. At operation, a gangrenous loop of ileum was found to have herniated behind a firm fibrous band which extended from the left pelvic wall to the region of the stump of vagina. The gangrenous portion of bowel was resected, and side-to-side ileo-ileostomy was performed.

Adherent loops of intestine may form unusual apertures.

Case 4—A woman, age 30, had undergone appendectomy for a ruptured appendix in 1922. In 1938, an acute obstruction of the small intestine suddenly developed. At operation, a loop of small intestine was found to be adherent to the terminal portion of the ileum. One end of the loop was attached to the mesenteric border and the other to the mesenteric border. Through this loop 6 cm. of ileum had herniated, causing obstruction.

Various apertures may occur in the omentum as a result of trauma or infection.

Case 5—A man, age 55, had undergone an operation for drainage of an appendiceal abscess in 1930, and later in the same year had undergone appendectomy. He was admitted to the clinic with an acute intestinal obstruction. At operation, a strangulated loop of ileum was found to have herniated through some adherent omentum in the right side of the lower portion of the abdomen. The edges of this aperture were thickened and fibrous. The obstruction was relieved by division and resection of this portion of omentum.

Paraduodenal Hernia—The literature pertaining to paraduodenal hernia is voluminous.^{1 3 6 9 10 11 12} An exuberant and diversified nomenclature has accumulated, with chaotic results, and the underlying facts seem to have been lost to complete analysis. Many fossae about the duodenum have been minutely described, but proof that they are a factor in the causation of such herniae is lacking.

Left duodenal herniae occur much more frequently than do those on the contralateral side. Bryan,² in 1935, stated that 162 of the former and only 43 of right duodenal herniae had been reported. Many of these herniae are never recognized during life and are found either at the postmortem table or accidentally when the abdomen is explored for other reasons. Such a state of affairs will be considered logical when it is realized that the herniae, as such, do not produce symptoms. It is only when obstruction, acute or chronic, or strangulation supervenes, that patients present themselves for treatment.

Diagnosis of a duodenal hernia is a rare feat. Of 91 cases of left duodenal herniae which Pikin⁷ collected, in only three was the condition diagnosed clinically. After careful analysis of his collected cases, Moynihan⁶ was able to offer some excellent suggestions which would permit a diagnosis to be made. In addition to the signs of acute intestinal obstruction, he noted that (1) a localized swelling of the abdomen will be present, the position of the tumor resulting from the side affected, and that around such a mass is a region of compression corresponding to the position of the colon, (2) the tumor may be distinctly delineated by palpation, and although sounding flat to superficial percussion, it will be rather resonant to deep percussion, (3) gurgling sounds may be heard anywhere in the tumor, and (4) in left duodenal herniae, because of the position of the inferior mesenteric vein in the neck of the sac, symptoms of venous obstruction may be evident. Blood may be found in the stool, hemorrhoids may be present, or dilated veins may be present on the anterior abdominal wall.

Eight "duodenal herniae" were encountered in the present series, and of these, six were on the left and two were on the right. Seven of the patients were men. The ages of these patients were between 32 and 59. In association with that which has been written previous to the production of symptoms, it is interesting to note that only two of these patients gave a history of abdominal pain and discomfort. It is likewise important to note that in one the duration of symptoms was 20 years and in the second, four years. Five of the herniae were discovered at operation for other pathologic conditions.

of the upper part of the abdominal cavity, whereas exploration in the remaining three patients was undertaken because of unexplained abdominal symptoms. Masson and McIndoe¹ have reported on one of the latter previously. Their patient had a large, right duodenal hernia, but the obstructive symptoms present were the result of a localized portion of hyperplastic tuberculosis in the ileum.

Case 6—A male, white, age 40, stated that he had had recurrent attacks of left abdominal pain for approximately four years. During the two years just prior to his registration, symptoms referable to intestinal obstruction were present. Tarry stools have been noted occasionally. During this period of four years, the patient had lost about 25 pounds (11 Kg).

Physical examination disclosed nothing abnormal save for abdominal tenderness over the region of the left portion of the colon. The patient had the sensation that an indefinite abdominal mass was present. Results of roentgenographic studies of the stomach and large bowel were normal, and a study for intestinal stasis revealed that the barium was distributed throughout the bowel in 16 hours. It was suggested that some unexplained type of pathologic process was present and that the latter might be either a diaphragmatic hernia or some other type of internal hernia. Surgical exploration was advised.

At operation a definite hernial opening was found at the duodenojejunal junction just under the ligament of Treitz. The opening to the hernial sac was closed. It is likewise interesting that a Meckel's diverticulum was also found in this patient.

Herniae Referable to Congenital Malformations—Instances of congenital malformation of the primary midgut loop, excluding the duodenal hernia, also form an interesting group. Such abnormalities have their origin in malrotations or improper fusion of the peritoneal layers, either of the mesentery of the small intestine, or of the cecum and ascending part of the colon. Persistent traction bands may also be found in such cases. Defective disposition of the small intestines and right part of the colon, a process commonly termed "malrotation," accounted for the production of hernia in two individuals. A report of one of the cases follows.

Case 7—The second of these patients was a boy, age three, who had been subject, since birth, to frequent episodes of vomiting, which had been marked during the first 18 months of life but which, during the year prior to the patient's registration, had occurred but once every two to four months. During these attacks the child would double up as if abdominal pain and cramps were present. Diarrhea or constipation was not noted.

The abdomen was moderately distended and an intestinal pattern was seen. However, peristalsis was not audible. Because of the persistence of regurgitation and the onset of other signs of partial high intestinal obstruction, the abdominal cavity was explored. The stomach, duodenum, and upper portion of the jejunum were distended, but the small bowel distally was collapsed. A persistent traction band, situated about eight inches (20 cm) from the ligament of Treitz, had almost completely occluded the jejunum. Associated with this anomaly was a clockwise malrotation of 90° of the postarterial segment of the primary midgut loop to the right. This malrotation had caused the cecum and ascending part of the colon to occupy their usual positions. However, the small bowel lay almost completely on the left side of the abdomen. The transverse part of the colon was anterior to the superior mesenteric vessels, whereas the jejunum lay

posterior to the tunks Symptoms probably were almost completely referable to the persistent traction band

Improper fusion of the peritoneal layers of the postarterial segment will result in the formation of small pouches under the cecum and ascending part of the colon Retrocecal hernia were found incident to performance of surgical procedures for other conditions in two patients Neither had had symptoms Reduction of the hernial mass, which may be composed of portions of the ileum, or ileum and cecum, is followed by simple suture of the orifice

Case 8—A second variety of paracecal hernia was found in a male, age 25, who complained only of moderately severe abdominal pain A region of extreme tenderness was present in the epigastrium Results of roentgenographic examination of the stomach were normal, but studies of the colon revealed that a transposition was present Upon exploration, a herniation of practically all the small intestine through an opening just beneath the ileocecal valve was found The aperture was large enough to admit three fingers An extremely mobile cecum was present Reduction of the hernia was accomplished by incision of the outer leaf of the peritoneum of the mesentery of the right part of the colon

In similar manner, prolapse of the ileum into a sac under the mesentery of the small intestine may also occur

Case 9—A male, age 34, had suffered recurrent attacks of pain in the right lower abdominal quadrant Acute appendicitis was the preoperative diagnosis, but exploration revealed an obliterated appendix Additional search demonstrated that a hernia involved 12 inches (30 cm) of ileum Additional interest in this case was provided by the presence of a Meckel's diverticulum

An internal hernia, involving the mesentery of the small intestine, but in a somewhat different situation than that just presented, may be found when prolapse of the bowel through an aperture lying between the ileocolic artery and its last mesenteric branch has taken place Such apertures may be either congenital or they may result from thinning of the mesentery caused by one of several factors The passage of a loop of intestine through such a hiatus is one of the more uncommon mechanisms producing acute intestinal obstruction

The occurrence of internal herniation through the foramen of Winslow is extremely infrequent, because of the barrier afforded by the transverse part of the colon In addition, the anterior and the posterior boundaries of the aperture are, as a rule, in direct contact According to Moynihan, one of the following factors must be present to permit the formation of this particular type of hernia (1) A common mesentery for the whole intestine, (2) absence of secondary fusion of the ascending part of the colon to the abdominal wall, (3) an abnormally large foramen, and (4) an abnormal length of the mesentery and consequent marked mobility of the intestine Pain experienced by such patients is usually epigastric and a tumor can usually be felt in the same situation A resonant note is obtained on deep

percussion over the mass. The usual signs of acute intestinal obstruction are present.

Case 10—Illustrative of herniation through the foramen of Winslow is the condition of a woman, age 56, who had suffered epigastric pain for three and one-half days. Nausea and vomiting were marked. On admission, considerable distention of the abdomen was evident and borborygmi could not be heard. Because of her poor physical condition, simple enterostomy alone was performed. The patient improved to such an extent during the succeeding 24 hours that further operation seemed indicated. The cecum and the ascending part of the colon were found to have prolapsed through the foramen of Winslow into the lesser peritoneal cavity. A condition which might be termed "hernia of a hernia" was also present, for part of the bowel had ruptured through the anterior leaf of the lesser omentum and was hanging down anterior to the stomach. This loop was distended and discolored. Decompression of the affected bowel was effected and the hernia was reduced. A catheter was sutured into the bowel at the point at which the gas had been withdrawn.

Miscellaneous Considerations—A few cases could not be satisfactorily classified in any of the above mentioned groups, so we have placed them in a miscellaneous group. There were four such instances, one of which already has been discussed in the section of this paper concerned with postoperative herniae into the broad ligaments.

Occasionally, secondarily to some inflammatory condition such as pelvic inflammatory disease, appendicitis, and the like, for which no surgical intervention has been undertaken, adhesive bands may form. In some instances, a Meckel's diverticulum may remain attached to the abdominal wall, producing a band-like structure. These bands and adhesions are occasionally the cause of herniation, with resulting intestinal obstruction.

It is difficult to explain the causation of mesenteric and omental defects and, in the absence of a suggestive cause, many are thought to be congenital. Rupture of either of these defects as a result of external violence and injury during the course of a previous operation are considered to be possible causes. In some cases, antecedent inflammation of the appendix with involvement and subsequent atrophy of mesentery or omentum may produce such a defect.

Stalker and Gray⁸ have previously reported a case of herniation into the prevesical space, or the space of Retzius. This was the sixth prevesical hernia to be reported in the literature. Several theories have been presented as to the origin of this type of hernia but in the absence of both trauma and a previous operation we feel that it must be considered to be secondary to some congenital defect.

Comment—Were it not for the fact that internal herniae become manifest through various degrees of intestinal obstruction, the majority of such herniae would pass without recognition. Occasionally, in performing an operation for some unrelated condition, an anomalous condition is found which may prove so confusing that it may seriously complicate the necessary surgical procedure. Inasmuch as these conditions may exist without producing symptoms, the surgeon should not attempt surgical repair in every case. As we

have pointed out, the majority of so-called para-duodenal herniae are not associated with symptoms. This is also true of certain of the herniae associated with malrotation of the colon. Extensive surgical intervention would be required to repair these congenital defects satisfactorily, and in many instances a satisfactory repair of the defect could not be accomplished. Thus, it is our conclusion that all general surgeons should be familiar with the anatomic aspects of various types of intra-abdominal herniae but that for the most part they should be conservative in their treatment when such herniae are found incidentally and are not producing serious symptoms. On the other hand, the presence of such herniae must be suspected in all cases of intestinal obstruction, either partial or complete. Treatment in these circumstances will be essential and will vary with the anatomic circumstances present at operation. Because such herniae frequently are associated with bizarre and not characteristic symptoms, their presence and the early recognition of the resulting obstruction of the small intestine may be overlooked. Because a preoperative diagnosis is seldom made, the problem of the correct treatment in the individual case may be difficult, and must be decided upon while the patient is on the operating table. In many of these cases strangulation is present and immediate surgical treatment must be instituted. It has been our experience that the various adjuncts in the treatment of intestinal obstruction, namely, an indwelling intestinal catheter, administration of 95 per cent oxygen and other conservative methods of intestinal decompression, have frequently been employed for undue periods for those patients who should have been operated upon immediately. Too great emphasis cannot be placed on the necessity of distinguishing accurately those conditions which are not amenable to such conservative treatment. It may be (and in this small group of cases of intra-abdominal hernia will be) impossible to make such a decision and, if doubt exists, fewer mistakes will be made by performing surgical exploration.

SUMMARY

Thirty-nine cases of intra-abdominal hernia, in which the patients were treated surgically at the Mayo Clinic between 1910 and 1939, inclusive, have been reviewed.

Eighteen herniae were considered to be primary, or directly the result of some congenital defect.

Twenty-one herniae occurred secondarily to operation, trauma, or inflammation. Symptoms were manifested by the herniae in 29 cases, and in ten cases the herniae were found incidental to operation for another condition. Some degree of intestinal obstruction was present in 28 cases, and in 19, acute intestinal obstruction developed. The histories of several patients illustrating the various types of intra-abdominal herniae found, have been presented.

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TESTICULAR TRANSPLANTATION

SUCCESSFUL AUTOPLASTIC GRAFT FOLLOWING ACCIDENTAL CASTRATION

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MILWAUKEE, WIS

PRESENTED BEFORE THE WISCONSIN UROLOGIC SOCIETY, BELOIT, WIS APRIL 30, 1938 AND AT THE NEW YORK ACADEMY OF MEDICINE, JANUARY 17 1940

LOSS OF THE TESTICLES in the adult as the outcome of criminal or punitive castration, traumatic accident and self-inflicted removal results in serious metabolic disturbances involving not only sexual functions but especially the nervous and muscular systems. Early recovery of the testicles with reimplantation into the scrotal region, observing certain physiologic considerations, offers the possibility of successful grafts. This procedure naturally is not applicable when surgical castration is performed for the removal of diseased testicles.

When the implanted tissue originates in the host it is called autogenous. The operation is termed autoplasmic transplantation or reimplantation. The transplanted tissue becomes a graft after evidence is present that it "takes" or survives.

In transplants, the survival of viable testicular cells is dependent upon nutrition resulting from the penetration of a compatible host's circulation into the transplanted tissue which consequently must be inserted in such form as to expose a large proportion of incoming cells to vascularization by the host. Reimplantation of the whole testis, or large portions of it into any part of the body has invariably resulted in little benefit and later sloughing. Tissue in the form of thin slices or mush injections are most apt to result in successful grafts.

Carl Moore's experiments have produced convincing proof that the testis attains its full development and functional capacity in the scrotum where the temperature is from three to six degrees below that of the internal parts of the body. A local tissue peculiarity in the scrotum may also be a factor in normal testicular development. The choice of the scrotum as the site for implantation is the *most important prerequisite* for success. The dartos layer is an ideal location for the introduction of transplants because of the total absence of fat, the presence of loose areolar tissue, the proper temperature and good vascularity.

The record of a patient observed over a period of two and one-half years is appended.

Case Report—On October 12, 1937, a hospital call from Dr. H. G. Oakland brought the author to the pathetic sight of a young man, age 23, whose right arm had been amputated just below the elbow, and both testicles, scrotum and the skin of the penis had been torn from his body. The accident had occurred less than one hour previously. While working in a box factory he had leaned forward over a lathe carrying a revolving knife



FIG 1—External genitals as they appeared after recovery from underwear

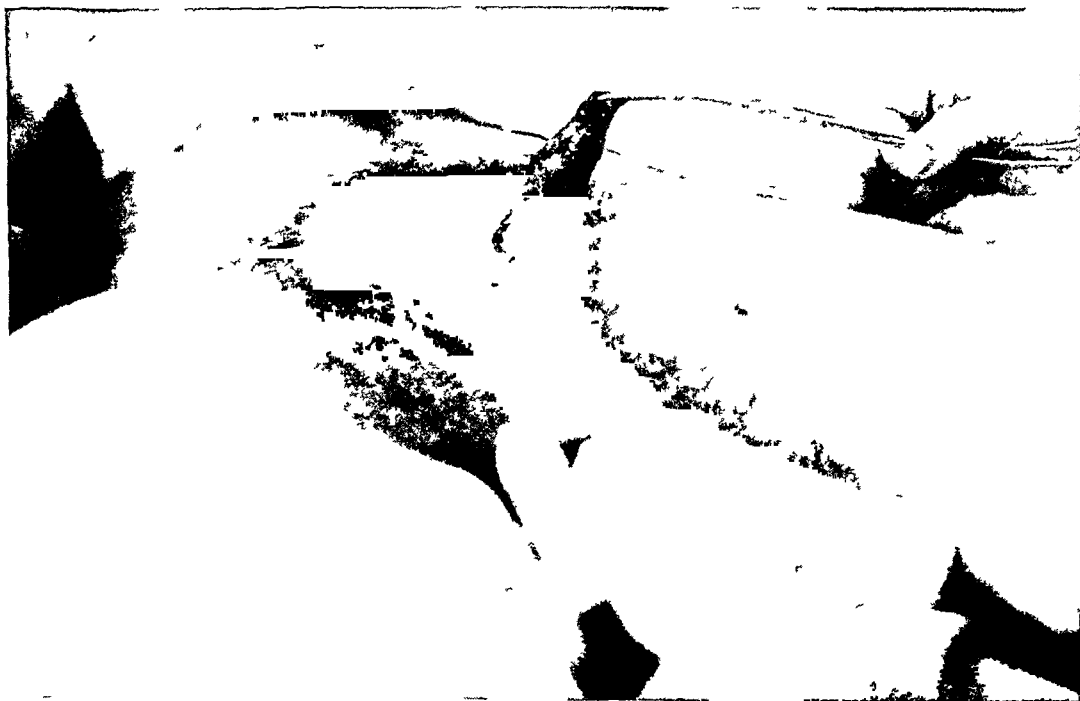


FIG 2—Appearance of the genitals before preparation for operation. The penis is denuded except for the semimucosal or inner part of the prepuce

when his trousers were caught up and quickly wound into the machine. His right hand grasped his trousers, was drawn into the whirling knife and amputated together with the external genitals. On arrival at the hospital he was in shock—severely exsanguinated. Doctor Oakland had controlled the bleeding in the arm stump. There was no bleeding from the genital wounds. With the aid of three blood transfusions during the night there was rapid recuperation.

The scrotal skin, intact testicles and the skin of the penis still attached to one another, were found in the patient's underwear and placed in a refrigerator overnight in a normal saline dressing (Fig 1).

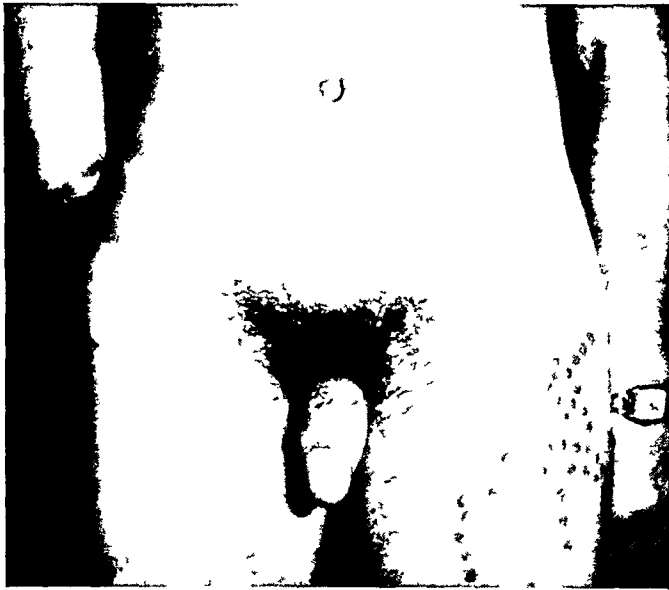


FIG 3—Photograph showing complete healing, with little distortion and full erectile function

The following morning, under general anesthesia, working concurrently with Doctor Oakland who repaired the arm stump, reconstruction of the genitals was carried out. Fourteen sliced cross-sections of testes, each about 2 Mm in thickness, were implanted in the scrotal wound and covered with the flaps of the remaining scrotal skin. One section of epididymis was also implanted.

The accident left the semimucosal or inner part of the prepuce still covering the glans (Fig 2). This part of the prepuce was simply inverted over the glans and covered about 3 cm of the distal part of the shaft, where it was held in place with a few interrupted catgut sutures. The remainder of the denuded penis was covered with a full-thickness graft made up of a collar of the very skin which had been torn from this area. All of the skin grafting was successful except the full-thickness one on the proximal part of the shaft which survived in only isolated areas and had to be largely replaced at several later sittings with pinch-grafts taken from the thigh. The patient left the hospital, December 14, 1937, apparently well, with a normally functioning penis (Fig 3).

Naturally, the pertinent questions concerning this patient are (1) Have the testicular transplants been successful, and (2) how long will the grafts function? For an answer to these questions one must consider the prostate gland which is the most sensitive clinical indicator of testicular function. Experimentally, in castrated male animals, the administration of androgenic agents is promptly followed by an increase in size of the atrophied prostate

and seminal vesicles. This reaction, in fact, is the basis of an assay method. Carl Moore Deansly, McCullagh and others have called attention to the prompt atrophy of the prostate following castration.

Subsequent Course.—True to form, our patient at the end of two and one-half weeks had developed a very definite shrinkage in the size of the gland. Instead of the usual succulent gland, typical of young men at his age, it had shrunken at this early post-operative stage to about one-half normal size. At the end of six weeks it was barely palpable and at three months could be outlined with difficulty by rectal palpation. Continued periodical rectal examinations revealed a gradual regeneration of prostatic tissue during ensuing months, indicating that the grafted testicular cells were surviving and probably elaborating secretion (Chart 1).

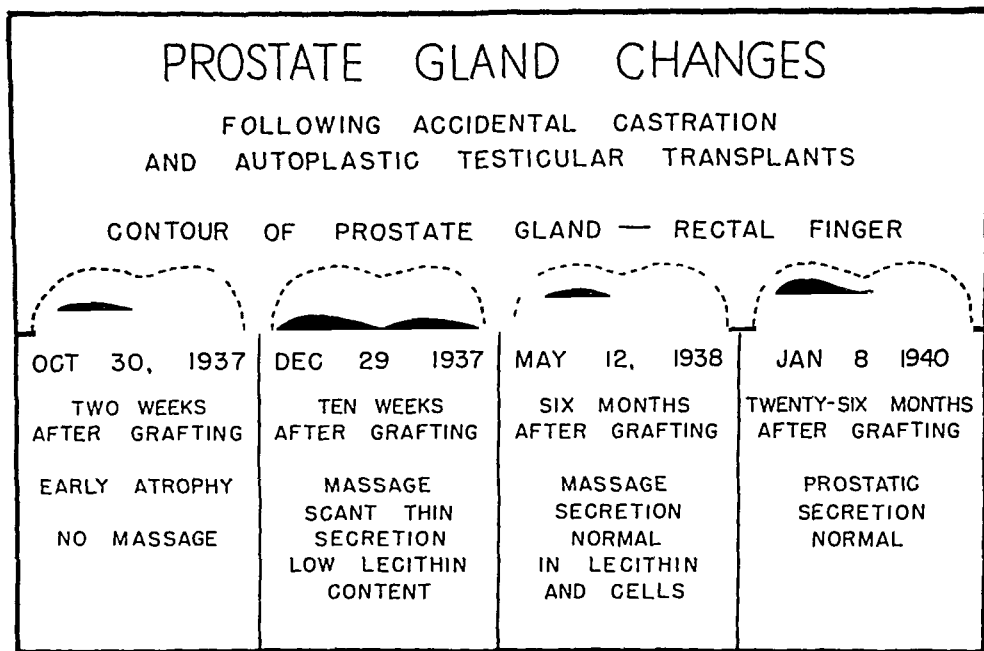


CHART 1

He has remained normal since that time, regained his full vigor and endurance, has normal libido and frequent erections, and has experienced ejaculations about once monthly. A number of definite nodules in the scrotal region at the site of the grafts, some the size of a pea, have persisted.

There has been no deviation from normal in numerous repetitions of the following tests: Friedman test for gonadotropin, basal metabolism test, blood cholesterol and sugar tolerance. Tests for the presence of androgenic hormones in the urine demonstrated increasing excretion of androgens. The last assay, completed August 19, 1939, showed an output of approximately 57 international capon units per day as compared to an output of 20 to 30 capon units per day during the first weeks following the operation (Chart 2). Because of the normal clinical course there has been no administration of either the extracts of thyroid, anterior pituitary-like substance or of testicular hormone at any time during his convalescence.

COMMENT.—The result in this patient has been very gratifying up to the present and we are hopeful that prolonged function will be realized. The grafted tissue in this patient possesses two essential qualifications for success. First, it is autogenous, being returned to its original host, and, second, it has been placed in its normal scrotal habitat. The early atrophy and then

regrowth of the prostate gland indicates that there was, primarily, a lack of cellular function but, later, adaptation and regeneration took place. The increasing urinary excretion of androgens now adds to the encouraging outlook.

The precautions required in tissue culture and transplantation were observed, namely. The reimplantation was carried out as promptly as possible after removal, sudden and repeated changes in temperature were avoided as well as direct exposure to sunlight, and there was no undue trauma or drying.

The successful result in this patient prompted an attempt to graft testicular tissue into human castrates. Homoplastic transplantation was recently performed on two castrates, who received injections under the scrotal skin.

RECORD OF TESTS ON GRAFTED CASTRATE J A							
DATE	BLOOD HEMOGLOB	FRIEDMAN GONADOTROPHIN TEST	BASAL METABOLISM	URINARY ANDROGENIC ASSAYS	BLOOD CHOLESTEROL	GLUCOSE TOLERANCE TEST	
NOV 6 1937	98%	NEGATIVE	93%	22 CAPON UNITS DAILY FIVE DAY COLLECTION	198 MGS	BLOOD SUGAR BEFORE 105.8 1/2 HOUR AFTER 184.3 1 HOUR AFTER 174 2 HOURS AFTER 150.4 3 HOURS AFTER 87.3	ONE HOUR URINE POS WITH 5 GTTS TWO HOUR URINE POS WITH 10 GTTS OTHERS NEGATIVE
DEC 15 1937	78%	NEGATIVE	161%	27 CAPON UNITS DAILY FIVE DAY COLLECTION	159.2 MGS	BLOOD SUGAR BEFORE 99 1/2 HOUR AFTER 186.9 1 HOUR AFTER 167.4 2 HOURS AFTER 98.5 3 HOURS AFTER 93	ALL URINE SUGAR NEGATIVE
APR 27 1938	80%	NEGATIVE	179%	44 CAPON UNITS DAILY FIVE DAY COLLECTION	127.9 MGS	BLOOD SUGAR BEFORE 101 1/2 HOUR AFTER 120.5 1 HOUR AFTER 113.6 2 HOURS AFTER 87.3 3 HOURS AFTER 73.2	ALL URINE SUGAR NEGATIVE
JAN 8 1940	94%	NEGATIVE	4%	57 CAPON UNITS DAILY FIVE DAY COLLECTION	183.1 MGS	BLOOD SUGAR BEFORE 102.6 1/2 HOUR AFTER 125.8 1 HOUR AFTER 149.3 2 HOURS AFTER 105.8	ALL URINE SUGAR NEGATIVE

CHART 2

of a testicular mush made up of the testicles of a young man killed in an accident. Preliminary blood grouping of donor and recipients was carried out. Their compatibility was established. This most important step is usually overlooked. A report on the results of these operations and others to follow will be published after several years of observation.

SUMMARY

(1) Autoplastic testicular transplants were carried out in a patient, age 23, following accidental castration.

(2) Successful graft resulted. Observation during two and one-half years demonstrated regeneration of the prostate gland, normal sexual behavior, and the persistence of normal clinical and laboratory tests.

(3) The method of transplantation herein described is recommended for the replacement of testicular tissue which is lost in the maneuvers of warfare.

THE PRESENT STATUS OF INTRAVENOUS FLUID TREATMENT OF TRAUMATIC AND SURGICAL SHOCK¹

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INTRAVENOUS fluid replacement therapy is one of the chief elements of modern shock treatment. The need for such replacement is evident because of the importance of oligemia in shock. This factor is of such importance that in the recently published British M. R. C. Memorandum, No. 1,⁷¹ "The Treatment of Wound Shock," the following statement was made: "It is now generally accepted that the most important requirement for arresting the progressive deterioration in general condition which is such a feature of shock, is restoration of blood-volume and thereby of tissue metabolism." In a recent definition of shock—progressive vasoconstrictive oligemic anoxia—one of us (H. N. H.) further emphasized the importance of the *oligemia* and inferred the need for prompt treatment before the *progressive* state had irreversibly injured the body by means of the *anoxia*.

Since the ideal method of correcting the oligemia would be to replace fluid exactly similar to that lost, this should be the ideal toward which therapy should be directed. It is difficult, however, in many cases to be sure just what blood elements have been lost and, even if known, such fluids are not always available. In some cases of shock, the fluid lost is essentially whole blood, in other instances, it is practically pure plasma. Various clinical cases run the entire gamut of possibilities between these two extremes. In other cases, more than one separate injury may be present—as, for example, a burn complicated by abdominal trauma and bleeding into the peritoneal cavity.

In the present paper, the various fluids that can be used intravenously in the treatment of shock are reviewed and the indications and contraindications for each are discussed. A few experimental observations on the fate of certain of the various fluids are cited. The fluids used may be listed as shown in Table I.

(I) SALINE CRYSTALLOID SOLUTIONS

These solutions have the advantage of ready availability, almost permanent preservability, and absence of toxicity, but recently a collection of evidence has been built up to show that in shocked patients their stay inside the blood vessels is only temporary. Furthermore, the more advanced the shock and the more imperative the need for treatment, the less apt are crystalloid solutions to be of benefit. Pilcher and Sollmann⁸² (1914), Krogh⁶³ (1922),

¹ Presented by title before the American Surgical Association, White Sulphur Springs, W. Va., April 28, 29, 30, 1941. To Doctor Harkins goes all credit for the work on this paper—Roy D. McClure.

TABLE I

PARTIAL LIST OF BLOOD SUBSTITUTES USED IN INTRAVENOUS RELIEF OF
THERAPY OF SHOCK

- (1) Saline crystalloids (normal salt solution Ringer's solution Locke's solution *etc.*)
- (2) Glucose solution
- (3) Gum acacia solution
- (4) Gelatin saline solution
- (5) Amino acid solution
- (6) Casein digestate
- (7) Ascitic fluid
- (8) Whole blood
 - (a) Direct transfusion
 - (b) Citrated fresh blood
 - (c) Citrated preserved blood
 - (d) Placental blood
 - (e) Cadaver blood
- (9) Plasma
 - (a) Natural plasma
 - (b) Reconstituted normal plasma
 - (c) Reconstituted concentrated plasma
 - (d) Calcificated plasma
 - (e) Heterologous (bovine) plasma
- (10) Serum
- (11) Red cell solution
- (12) Hemoglobin Ringer solution

Kinsman, Spurling, and Jelsma⁶¹ (1928), Miller and Poindexter⁷² (1932), Roberts and Crandall⁸⁴ (1933), Adolph, Geibas, and Lepore¹ (1934), Horsley⁵⁵ (1934), Amberson³ (1937), Hepler and Simonds⁴⁹ (1938), and Wakeley⁹³ (1940) noted the ease of escape of these solutions from injured blood vessels. Whitby⁹⁵ (1941) stated "The effect of saline is evanescent." Best and Taylor¹¹ (1939) also recognized the short stay of crystalloid solutions in certain surgical cases, stating "If the blood volume has been reduced as a result of hemorrhage or shock, the intravenous injection of a saline solution, owing to the short stay of this fluid in the blood stream, is of little value, and may indeed be harmful. Transudation of fluid into the tissue of the lung—pulmonary edema—may result."

Hill, McMichael, and Shaipey-Shafer⁵⁰ (1940) also made observations on the transiency of action of crystalloid solutions. They found that "physiologic or hypertonic saline given intravenously to normal people is rapidly lost from the circulation" and that "in shocked patients intravenous saline produces transient benefit only." Similar observations were made by Maes and Davis⁷⁰ (1941), stating "When the reduction in blood volume has existed long enough to produce, through oxygen lack, increased permeability of the capillary walls, administration of such solutions may result in a further loss of plasma proteins from the blood stream." These authors pointed out that advocacy of crystalloid solutions in shock treatment by MacFee and Baldridge⁶⁷ (1930) and by Hoitink⁵³ (1935) may depend on a consideration of cases seen before marked increase in capillary permeability has occurred.

Davis^{33, 34} (1937) performed experiments which indicated that excess use of crystalloid solutions may be harmful in shock. A diminution in oxygen usage occurred in such cases which Davis termed an "anoxemic response."

The most complete exposition of this aspect of the subject, however, was

made by Blalock, Beard,^{8, 9, 10, 13, 14, 15} and then associates (1932 and 1933) in a series of six experimental papers. They found that saline or glucose injections would actually wash plasma proteins out of the blood stream, causing the animals to be poorer in plasma protein than they would have been if not treated at all. Further extensive studies of Minot⁷³ (1937), and of Minot and Dodd^{74, 75} (1940 and 1941), have corroborated these observations. Minot and Dodd⁷⁴ (1940) stated "When plasma protein is deficient, the administration of fluid alone fails as a means of restoring an adequate volume of blood. Indeed, such measures often result in a greater loss of protein through injured capillaries."

Buttle, Kekwick, and Schweitzer²⁴ (1940) performed a series of experiments shown in Table II. These experiments indicated that isotonic saline easily passes from the circulation into the tissues and is unable to raise the blood volume for more than a brief time. Cats were bled 50 per cent of their calculated blood volume as rapidly as was compatible with life, and then the blood volume was restored with various blood substitutes. It is seen that not only all of the untreated controls, but all the saline injected animals died. It is also seen that of the 12 blood substitutes tested, only three (plasma, dried plasma of Greaves, and filtered plasma) were as efficacious as whole blood in restoring the blood pressure of cats in shock to normal. It is also seen from the table that only seven of the 12 saved the lives of all the cats tested. Buttle and his associates rated the blood substitutes in the following order of merit: Plasma, serum, hemoglobin-Ringer, gum acacia, red cell solution, isotonic saline, and last isotonic glucose.

TABLE II

EXPERIMENTS OF BUTTLE, KEKWICK, AND SCHWITZER (LANCET 2:507, 1940) ON RELATIVE MERITS OF DIFFERENT BLOOD SUBSTITUTES IN RESTORING BLOOD PRESSURE OF CATS RAPIDLY BLED 50 PER CENT OF THEIR BLOOD VOLUME

Fluid Replaced	No of Expts	Deaths	Av Vol of Fluid Given (cc)	Blood Pressure Response
(1) None	7	7	None	None
(2) Whole blood	5	0	83	Good and maintained
(3) Normal salt	5	5	95	Poor and transient
(4) Normal glucose	5	5	89	Poor and transient
(5) Acacia	8	3	93	Fair with slight later fall
(6) Hemoglobin Ringer	5	0	75	Good with slight later fall
(7) Cells	6	3	75	Fair but temporary
(8) Plasma	7	0	70	Good and maintained
(9) Serum	7	0	72	Good with slight later fall
(10) Dried serum	3	0	66	Fair and maintained
(11) Dried plasma (Davie)	6	6	25	All died at end of injection
(12) Dried plasma (Greaves)	3	0	79	Good and maintained
(13) Filtered plasma	5	0	81	Good and maintained
(14) Plasma-saline	3	0	69	Poor with later fall

At the Henry Ford Hospital one of us (H. N. H.) performed experiments that will be reported in detail elsewhere in which an attempt was made to measure the amount of saline which when infused in the presence of shock will leak out into the local area of trauma. It is known, as seen in Chart 1, that when one hind limb of a dog is traumatized, about 42 per cent body

weight of plasma-like fluid is lost into the limb up to the time of death, as shown by Parsons and Phemister⁸¹ (1930). Similar mechanical trauma, followed by intravenous infusion of 1,980 cc of normal saline solution, resulted in an excess in weight of 6.3 per cent body weight indicating that about 16 per cent of the infused saline leaked out into the local area of trauma. Because of the small amount of urine (160 cc) and the low bleeding volume (2.5 per cent body weight), the rest of the saline must have escaped into the tissues generally throughout the body. In other similar experiments, the excess in weight of the traumatized limb in saline treated dogs was as much as 10 per cent body weight. As seen in Chart 2, saline also leaked out into

<u>EXPERIMENT</u>	
<u>TRAUMA + SALINE (4-19-40)</u>	
DOG WEIGHT = 15.0 KGM	
TRAUMA 5 05 PM	
GIVE 1980 cc SALINE	
BLEED TO DEATH AT 2 AM	
BLEEDING VOLUME = 375 cc	
(= 2.5% B W)	
URINE = 160 cc	
EXCESS WGT TRAUMATIZED SIDE	
= 950 GM (= 6.3% B W)	
(UNTREATED DOG EXCESS = 4.2% B W)	
2.1% B W = 315 cc OF SALINE	
GIVEN WAS LOST LOCALLY AT SITE OF	
TRAUMA, OR ONLY 16% OF TOTAL	

CHART 1—In this typical experiment, it is demonstrated that when one side of an anesthetized animal is traumatized and saline is afterward given intravenously, the traumatized limb exceeds the opposite normal limb by an amount equaling 6.3 per cent body weight. When compared with the average 4.2 per cent body weight excess of similarly traumatized limbs not treated with saline, it is seen that about 16 per cent of the saline administered leaked out into the traumatized area.

the locally traumatized area in a case of shock due to subcutaneous bile salt injection. In Chart 3, it is seen that even whole blood when transfused probably causes some increased fluid to leak into the traumatized area. The fact that 37 per cent of the injected volume did so, as opposed to only 16 per cent in the two illustrative saline injection cases, is not taken to mean that blood is more likely to leak out in the locally traumatized area than saline. Rather, it is linked up with the smaller absolute volume of blood given and also it is considered to mean that less of the fluid is lost away from the site of trauma.

(2) GLUCOSE SOLUTION

Practically all of the objections to saline apply equally well to glucose. Murphy, Correll, and Grill⁷⁸ (1941), in studying the effects of intravenous

solutions in patients with and without cardiovascular defects, observed dangerous reactions after the use of 50 per cent glucose solution

(3) GUM ACACIA SOLUTION

Colloid solutions were used intravenously by Czeiny¹² (1894) Hogan⁵² (1915) made the first clinical use of these substances, injecting 2.5 per cent gelatin solution. Gum acacia was used clinically by Hurwitz⁵⁸ (1917) and

<u>EXPERIMENT (6-28-40)</u>	
<u>SUBCUTANEOUS BILE + SALINE</u>	
DOG WEIGHT = 11.7 KGM	
INJECT BILE 4 25 P M	
GIVE 2575 cc SALINE	
DEATH ABOUT 2 A M. (6-30-40)	
WATER PER OS = 1100 cc	
URINE = 3310 cc	
EXCESS WGT INJECTED SIDE	
= 850 GM (= 7.3% BW)	
(UNTREATED DOG EXCESS = 3.8% BW.)	
3.5% B.W OR 409 cc OF	
SALINE GIVEN WAS LOST LOCALLY AT SITE	
OF TRAUMA, OR ONLY 16% OF TOTAL	

<u>HEMATOCRIT</u>	
INITIAL _____	46
BEFORE SALINE _____	51
AFTER SALINE _____	32
FINAL _____	55

CHART 2—In this typical experiment it is seen that about 37 per cent of the blood administered to a traumatized dog leaked out into the local area of trauma

popularized by Bayliss⁷ (1917). Since then it has been used by many, but recently adverse reports as to its toxic effects have been written by Dick, Waiweg, and Andersch³⁶ (1935), Christie, Phatak, and Olney²⁹ (1935), Studdiford⁹⁰ (1937), Hall⁴⁵ (1938), Cattell²⁵ and associates (1939), and by Hendrick, Keeton, and Foley⁶⁰ (1938). Extensive deposition in the liver is one of the drawbacks of acacia. Acacia may remain in the body for months as shown by Andersch and Gibson⁴ (1934), or even for years as demonstrated by Keith, Power and Wakefield⁵⁹ (1935).

In the controlled experiments of Buttle²⁴ and associates (1940) on cats, three different samples of gum acacia solution were tested. Immediate recovery in all the animals was good, but there was a tendency for the blood pressure to fall after the infusion ended and three, of the eight animals tested, died. The fall of blood pressure may be explained in part by the fact that acacia leaves the blood stream easily as claimed by Amberson³ (1937), but Buttle²⁴ and associates believe it is more likely due to specific action of the gum on the vessels causing dilatation and increased capillary permeability as originally claimed by Drinker³⁸ (1927). Buttle²⁴ and his coworkers con-

cluded that "the effects of gum-saline were much better than those of saline or glucose, but were not as good as those of whole blood"

(4) GELATIN-SALINE SOLUTION

This method was used by Hogan⁵² (1917) and was recently revived by Chambers²⁶ (1941) in his experimental studies. It may prove of value in the future.

<u>EXPERIMENT</u>	
<u>TRAUMA + TRANSFUSION (3-1-40)</u>	
DOG WEIGHT = 20.4 K G M	
TRAUMA 4:41 PM	
GIVE 780 cc BLOOD	
DEATH AT 1:05 AM	
BLEEDING VOLUME (BLALOCK) = 175 cc.	
(= 0.85 % B W)	
URINE = 0	
EXCESS WGT TRAUMATIZED SIDE	
= 1150 GM (= 5.6 % B W)	
(UNTREATED DOG EXCESS = 4.2 % B W)	
1.4 % B W OR 286 cc OF	
BLOOD GIVEN WAS LOST LOCALLY AT SITE	
OF TRAUMA, OR ONLY 37 % OF TOTAL	

CHART 3—In this typical experiment it is seen that about 16 per cent of the saline administered to an anesthetized dog with shock due to subcutaneous bile injection leaked out into the local area of trauma.

(5) AMINO-ACID SOLUTION

Several articles refer to this solution, but since a casein hydrolysate is used in most cases, this will be considered in the next section.

(6) CASEIN DIGESTATE

Casein is used because it contains all of the 11 essential amino-acids. Elman and Weiner⁴¹ (1939), Fall, Emerson, and Fletcher⁴⁴ (1940), and Elman^{42, 43} (1940) in two papers discussed this mode of therapy. Madden, Zeldis, Hengeier, Miller, and Whipple⁶⁸ (1941) and later Madden⁶⁹ (1941) studied the utilization of a casein digestate injected by vein in forming plasma proteins. By an established technic for the measurement of plasma protein production in hypoproteinemic dogs, these authors determined that an enzymatic (papain) digest of commercial casein (Lilly) given parenterally is as effective in plasma protein production as whole liver by mouth. The golden yellow granular material containing 12.5 per cent protein is made into a 5 per cent solution and when given either intramuscularly or subcutaneously is well-tolerated. As much as 16 Gm of the digestate was given in four minutes. These authors concluded that "certain *digests* given by vein or subcu-

taneously *promote new plasma production* as effectively as protein fed by mouth" (Italics are those of Madden,⁶⁸ *et al*)

(7) ASCITIC FLUID

Ascitic fluid was used experimentally in shock treatment by Davis and White³⁵ (1938), Choisser and Ramsey^{27 28} (1938, 1939), and by Mulder, Davis, and Streeter⁷⁷ (1939) This latter group of authors applied the lyophile principle of ascitic fluid, redissolving the dried fluid in water and injecting it in, usually a two and one-half times original concentration Maes and Davis⁷⁰ (1941) have recently reported on the use of ascitic fluid in 22 transfusions in human beings with good results Providing that enough ascitic fluid is available, this method of treatment may prove of value in the future

Holubec⁵⁴ (1940) stated that Meeson and Čukanowa (1936) had already reported the clinical use of ascitic fluid transfusions in 60 cases Holubec⁵⁴ used as donor a patient age 42 with mitral stenosis The ascitic fluid had a specific gravity of 1.019 and was used with good results in combination with preserved blood in the treatment of five cases of shock

(8) WHOLE BLOOD

Papers on this subject are so numerous that only the reviews of V Ziemsens⁹⁷ (1892), Rossius⁸⁵ (1925), Doan³⁷ (1927), Vary⁹¹ (1940), Harkins⁴⁶ (1941), and Hoxworth and Skinner^{56 57} (1941) will be cited Several types of blood are usable

(a) *Direct transfusion*—This type of administration is valuable, but its practical difficulty outweighs any theoretical advantage it may have In time of war its usefulness is still further narrowed

(b) *Citrated fresh blood*—This blood has great usefulness, but in time of war is not as valuable as

(c) *Citrated preserved blood*—With modern methods of blood preservation, as discussed in the review of Harkins⁴⁶ (1941), this type of blood more than makes up in practicability any theoretical disadvantages it may have

(d) *Placental blood*—This type of blood can never be used on the large scale demanded by wartime Placental blood samples are furthermore, frequently infected

(e) *Cadaver blood*—This method is especially used in Russia by Youdine⁹⁶ (1936) One of us (H N H) visited Professor Youdine's clinic in 1939 and saw cadaver blood transfusions in actual use The reaction rate is slightly higher than with citrated blood and the method also requires a larger number of fresh cadavers than is found in a single hospital in practically any city in this country

Importance of hemoglobin—Another point to consider in choosing between different methods of shock treatment is the relative importance of the quantitative reduction in blood volume and any qualitative alteration in the patient's hemoglobin content Brodin and Saint Girons²⁰ (1939) believed

that the blood volume decrease and not the anemia is of prime importance in shock. Maes and Davis⁷⁰ (1941) have emphasized the relative unimportance of lack of hemoglobin itself in cases of shock. In advocating ascitic fluid injections they stated "Despite the fact that ascitic fluid contains no hemoglobin, its use in states associated with acute loss of whole blood is rational, as in such states there is usually enough hemoglobin remaining to carry on the respiratory functions of the blood. Only 3 Gm of hemoglobin per 100 cc of blood is necessary to maintain adequate oxygenation in the mammalian organism." To draw a simile, if a traffic jam has interfered with transport of food to a starving town, it is much more important to enable the trucks present to move more rapidly than to add more trucks. Thus, if in shock the blood flow is reduced to one-fifth normal, increasing the red cells by a one-fifth will be only one-twenty-fifth as effective as bringing the blood flow up to normal.

Black and Smith¹² (1941), in discussing the relative merits of whole blood and plasma in the treatment of bleeding peptic ulcer, stated "In general terms, plasma is contraindicated when the hemoglobin is less than 50 per cent." Some such compromise course as this would seem to be better than advising plasma in all shock cases. In the past two years, the pendulum has swung so far in the direction of using plasma that surgeons pay more attention to what they are injecting than to the needs of the patient. There is much truth to Strumia's statement⁸⁸ (1940) that there is only one emergency condition—carbon monoxide poisoning—in which whole blood has a marked advantage over plasma, but extremes should be shunned. Perhaps the best rule for blood substitutes is to actually substitute what is lost. Where blood is lost, give blood; where plasma is lost, give plasma.

TABLE III

METHODS OF CALCULATING TRANSFUSION DOSAGE	
(1) Method of Elkinton, Wolff, and Lee ⁴⁰ (1940)	Based on blood concentration and plasma protein level. Especially applicable to burns.
(2) Method of Bushby, Kekwick, and Whitby ²³ (1940)	Comparing the blood concentration before and after a test plasma infusion.
(3) Method of Hill ⁵¹ (1941)	Comparing the blood concentration before and after a test cell infusion.

Methods of calculating transfusion dosage—Several methods have been published of accomplishing this in patients without directly determining the blood volume. The method of Elkinton, Wolff, and Lee⁴⁰ (1940) is especially applicable in burns or other instances of pure plasma loss. As seen from Table III, it depends on observation of the hematocrit and plasma protein concentration. The method of Bushby, Kekwick, and Whitby²³ (1940) is also listed in the table. Hill⁵¹ (1941) has another method of measuring the amount of fluid necessary to give in shock. He does this by a simple method of calculating the blood volume which is then compared with the normal blood volume of a patient of that size. The difference between the normal and the

actual blood volumes indicates the amount of fluid that it is necessary to give. The initial blood volume is calculated as follows

$$\begin{aligned} BV_1 &= \text{Initial blood volume} \\ Hb_1 &= \text{Initial hemoglobin of patient's blood} \\ Hb_2 &= \text{Hemoglobin of infused cell solution} \\ Hb_3 &= \text{Final hemoglobin of patient's blood} \\ c &= \text{Volume of cell solution} \\ BV_1 &= \frac{c (Hb_2 - Hb_3)}{(Hb_1 - Hb_3)} \end{aligned}$$

The more concentrated the red cell solution is, the more effect a given amount will have and the more accurate the computed result will be. This method is the exact opposite of that of Bushby, Kekwick, and Whitby²³ (1940). The cell solution may be harder to give, but is less apt to leak out and vitiate the results.

(9) PLASMA

Buttle²⁴ and associates (1940), speaking of a 50 per cent hemorrhage, stated "In hemorrhage of this degree replacement of red cells plays no vital part in treatment. Replacement with plasma gives as satisfactory a result as replacement with whole blood." In their cat experiments, there were no deaths in the plasma treated series and in all instances the blood pressure not only rose to normal but the level was maintained.

Plasma has been used in one form or another for several years and the results have been reported by many writers. Reference will be made to the review by Harkins⁴⁶ (1941) for the bibliography, and to the note by Brennan¹⁸ (1941). Plasma is used in several forms, as follows:

(a) *Natural plasma*—This has the advantage that it can be obtained from blood banks in large quantities. It is especially useful in the treatment of burns. That the use of plasma is not a new idea is testified by quotation of the following letter appearing in the March 9, 1918, number of the British Medical Journal:

"TRANSFUSION OF PLASMA

"Sir,—I have been reading with interest recent articles in the Journal on blood transfusion in casualty clearing stations. Apparently one of the chief troubles is the question whether or not the recipient's plasma will haemolyze the corpuscles of the donor.

"Surely this difficulty might be avoided by not transfusing the corpuscles at all, but only citrated plasma, which would be easy to keep and easy to give. There is abundant clinical and experimental evidence that it is not the corpuscles that are wanted, but the ideal fluid for keeping blood pressure at its proper level, and the apparent advantage of blood is, no doubt, due to its permanent value in this respect and to its food value. A man apparently dying from haemorrhage is not dying from lack of haemoglobin, else severe cases of anaemia would die long before they do, but from draining away of fluid, resulting in devitalization and low blood pressure.

"May I at least recommend a trial of this method, controlled, let us say, by an equal number of whole blood transfusions and an equal number of gum acacia (not less than 6 per cent) cases?—I am, etc.,

"Sevenoaks, March 3

Gordon P. Ward,

Captain R. A. M. C. (S. R.)"

(b) *Reconstituted normal plasma*—This is plasma that has been dried and is then diluted with water up to its original concentration. Vaughan⁹² (1941) and others have pointed out that when such plasma is filtered and allowed to stand it tends to clot more than unfiltered plasma. The use of dried plasma has recently been reviewed in an editorial³⁹ in the *Lancet* (1941) and in an article by Harper⁴⁷ and coworkers (1941). At the Henry Ford Hospital, we have used reconstituted plasma dried by the rotor evaporator of Haitman⁴⁸ (1940).

(c) *Reconstituted concentrated plasma*—This is usually given in four times normal concentration.

(d) *Calcificated plasma*—Clegg and Dible³⁰ (1940) convert their plasma into serum by adding calcium chloride. Experiments on this conversion at the Henry Ford Hospital indicate that the titration sodium citrate = calcium chloride is not always simple and that this method may lead to uncertain results.

(e) *Heterologous plasma* The use of bovine plasma in particular has been studied by Cohn³¹ (1940) and by Wangenstein, Hall, Kremen, and Stevens⁹⁴ (1940). Kremen, Hall, Koschnitzke, Stevens, and Wangenstein⁶² (1941) recently reported on their results with administration of bovine plasma intravenously to man. The fluid contained 0.3 per cent sodium citrate and 20 mg per cent sulfanilamide as a final concentration. It was given after skin tests and gradual desensitization, even in the cases with negative skin tests. With this material in unit doses of 250 cc, 119 patients were treated. Two cases of shock were treated, including a case of bleeding peptic ulcer and as much as 2,500 cc was given to three cases. There were no deaths, but three anaphylactoid reactions occurred. Savage, Taylor, and Keys⁸⁶ (1941) studied the sensitivity to various heterologous plasmas and found that dog and fox plasmas cause most reactions in man of those tested (cow, goat, rabbit, sheep, horse, human, dog, and fox). Cow plasma gave no more positive skin tests than did human plasma. Another point of interest was that just because a person was sensitive to one plasma did not mean that he would be to those of other species.

(10) SERUM

The relative merits of serum and plasma are frequently discussed of late. In general, plasma is more apt to develop fibrin deposits, while serum is said to be more toxic. Buttle, Kekwick, and Schweitzer²⁴ (1940) found, in their controlled experiments on cats in which plasma effected recovery, serum caused only a temporary improvement in blood pressure. Furthermore, a severe reaction occurred in five out of seven cats. Such reactions after serum were noted by Biddle¹⁹ (1900). Buttle²⁴ and associates concluded that "some toxic substance absent from plasma was present in serum." The literature on the question of liberation of physiologically active substances in serum was reviewed by Amberson⁷ (1937) who stated "Blood plasma is to be preferred to serum because of the formation, in the latter, of vasodilator or constrictor

substances produced in the act of clotting" A similar conclusion was reached by Doan³⁷ (1927) Biodin and Saint Grions²⁰ (1939) Scuddei⁸⁷ (1940), and by Struma, Wagner, and Monaghan⁸⁹ (1940)

Serum as opposed to plasma is not without its supporters, however Its use is favored by Levinson, Neuwelt, Rubovits and Necheles^{65 66} (1940), Clegg and Dible³⁰ (1940), and by Brown and Mollison²² (1940) Concentrated serum was used in burn treatment by Qvist⁸³ (1941) In his recent Greensfelder Lecture, Blalock¹⁶ (1941) pointed out that at present the shift is toward the use of serum

At present, very little natural serum is used and as far as we are aware, no heterologous serum has been administered clinically Main emphasis has been placed upon reconstituted dried serum, either in the normal or concentrated form Serum has been used by Aldrich² and associates (1938), Bond and Wright¹⁷ (1938), Lehman⁶⁴ (1939), and others cited above Brown²¹ (1941) was unable to confirm the results of Aldrich² and associates (1938) on the value of concentrated serum in nephrosis

Hill, McMichael, and Sharpey-Schafe⁵⁰ (1940) found that, as already cited, crystalloid solutions increase the blood volume only temporarily in normal persons or in shocked patients On the other hand, they stated that "Serum given intravenously to normal people is retained in the circulation for long periods The rise in blood volume depends on the total quantity of protein added, and is independent of the dilution of the serum employed," and "Intravenous serum is very effective in overcoming circulatory collapse due to diminished blood volume"

(11) RED CELL SOLUTION

Buttle²⁴ and associates (1940) injected a red cell suspension into cats in their controlled experiments The immediate recovery after transfusion was good, but the blood pressure tended to fall and respiration was much disturbed in all experiments Three of the six animals died Rossius⁸⁵ (1925) reported that red cells exert about the same resuscitating power as saline in the treatment of acute hemorrhage It would seem advisable, at present, to reserve the use of red cells left over in blood banks for treatment of chronic anemic states rather than of acute traumatic shock Mollison⁷⁶ (1941) advised against the use of red cell solutions of over seven and one-half million cells per cubic mm because of the factor of increased viscosity

(12) HEMOGLOBIN-RINGER SOLUTION

This solution has been mainly used for experimental purposes Amber son³ (1937) stated that it has the following advantages as a blood substitute It exerts a high colloidal osmotic pressure and the dissolved hemoglobin takes up oxygen and stimulates hematopoiesis Buttle²⁴ and his associates (1940) used a solution containing 3.7 Gm of oxyhemoglobin per 100 cc The immediate recovery of the blood pressure was good, but there was a tendency for it to fall during the period of observation and to be highly unstable Respira-

tory disturbances were frequent. These authors concluded that this solution gives uncertain results which are not as good as those of whole blood, but which are better than those obtained with acacia. This solution is also apt to lead to renal tubular occlusion as shown by Amberson (1937), Baker and Dodds⁶ (1925) and Aubertin⁵ and his colleagues (1939). The use of hemoglobin-Ringer solution in four patients with anemia was reported by O'Shaughnessy, Mansell, and Slome⁸⁰ (1939). After preliminary alkalinization of the urine, amounts of 200, 250, 600, and 1,000 cc of 5 per cent solution were given intravenously in an hour or less to four patients respectively.

CONCLUSIONS

(1) Saline and glucose solutions are unsuitable for blood substitutes because they are lost so quickly from the damaged vessels.

(2) Plasma and serum are at the present time the best substitutes for whole blood and in some cases are better than blood itself. In cases of marked anemia, whole blood is preferable.

(3) Use of ascitic fluid, bovine plasma, and casein digestates may be of value in the near future, but such use is still in the experimental stage.

(4) Adequate dosage computed by the methods outlined in the paper, or by similar means, is essential.

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CLINICAL SIGNIFICANCE OF PROTHROMBIN DEFICIENCY AND ITS TREATMENT

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THE DISCOVERY of vitamin K has led to renewed interest in the mechanism of blood clotting, a field of study which for years has baffled many investigators. Indirect methods for the measurement of plasma prothrombin concentration have been developed, and as a result the clinical importance of prothrombin deficiency has also been brought under study. According to current ideas, plasma prothrombin, ionized calcium, and a tissue or platelet factor, thromboplastin, interact in the first phase of clotting with the formation of thrombin. Thrombin then acts upon plasma fibrinogen and fibrin is laid down. The process is known to be influenced by temperature, p_H , electrolyte pattern, and colloid content of the medium, as well as the concentration of the four primary clot factors. The nature and mode of action of the physiologic anticoagulants is as yet undetermined, but there is good reason to suppose that such substances exist and that their effect may be exerted against either or both of the two phases of clotting. The place of heparin in physiologic clot inhibition and the manner in which it acts are questions still unanswered, though the subject is being intensively investigated.

It has not been determined to what extent clotting is an enzyme reaction, and, indeed, the nature of the clotting mechanism must stand in clear relief before such intimate analysis will be possible. There can be no doubt, however, that the speed of clotting under physiologic conditions is directly related to the concentration of thrombin. The concentration of thrombin further depends on the concentration of prothrombin, though variables come into consideration at this point. The speed of formation of thrombin from prothrombin is influenced by concentration of thromboplastin, ionized calcium and antiprothrombic agents, and possibly by inherent "convertibility" of the individual's prothrombin,^{1, 2} a rather vague conception. The rapidity of clotting is obviously of the utmost importance in determining the hemostatic value of the process, but a neglected subject, of equal or greater importance, concerns the factors affecting the quality of the formed clot. Those who have worked with plasma clotting, in which the gross physical characteristics of the clot can be readily observed, know that the fibrin mass may be soft and jelly-like, tough and opaque, adherent or slippery, granular, friable, or noncontractile. These qualities are not necessarily related to the speed of clotting, but probably depend in part, at least, on the concentration and quality of the fibrinogen.

Methods of Measuring Plasma Prothrombin Concentration—Though knowledge of the coagulation reactions is incomplete, nevertheless, there can be no doubt about the clinical value of prothrombin determinations as performed by recently developed methods. As previously noted, these methods are indirect, for prothrombin cannot be isolated and weighed, or brought into definite measurable chemical combinations. The two methods which, in their original or modified forms, have been most widely used in this country are the two-stage titration method of Warner, Binkhous, and Smith,^{3 4} and Quick's method of measuring clotting time of plasma in the presence of optimal concentration of calcium and thromboplastin.^{5 6} The first is more complicated, but results in better control of the variables and yields more precise data. The two-stage technic is preferable in investigative work, while Quick's method is more practical in controlling the administration of vitamin K clinically. Quick's method has been variously modified by using sodium citrate as the anticoagulant instead of sodium oxalate, by varying the amount of calcium chloride used in recalcification, by using thromboplastin from different sources, by serial dilution of the plasma, and by expressing the results in different terms. It should be borne in mind in using the Quick method that a linear relationship does not exist between prothrombin concentration and the plasma clotting time, and that it is, therefore, not permissible to convert clotting time directly into percentage of the normal control value. The "bedside method,"² in which the determination is made on freshly drawn whole blood, thus obviating the use of anticoagulants and the centrifuge, in the author's experience, gives rather variable results, though it yields more significant information than does the ordinary determination of clotting time. Methods have been proposed for studying the prothrombin content of infants' blood which avoid the need for venepuncture by using small amounts of blood from a stab wound, and apparently such methods yield clinically helpful data.^{7 8}

Occurrence of Prothrombin Deficiency—An examination of the known facts of vitamin K metabolism suggests clinical and experimental states in which the normal rôle of this accessory food factor may be disturbed. Vitamin K occurs naturally as a fat-soluble substance or substances, rather widely distributed in leafy green vegetables and in certain animal tissues. Its proper absorption, like that of other fat-soluble vitamins, depends on the presence of sufficient amounts of bile salts in the small intestine. Absorption from the colon probably does not occur. After absorption from the intestine vitamin K conditions, in some as yet unknown manner, the formation of prothrombin by the liver. Prothrombin is a constituent of the plasma globulin, and apparently both vitamin K and prothrombin are not stored to any significant extent in the body. From this one might expect prothrombin deficiency as a result of insufficient intake of vitamin K, lack of bile salts in the intestine with or without jaundice, impaired absorption of nutrients from the intestine as in diarrheal states, and defective digestion and absorption of fat due to lack of pancreatic enzymes. In addition, prothrombin deficiency might, theoretically, be based on impaired liver function from intrinsic liver disease, with conse-

quent failure in utilization of vitamin K. Prothrombin deficiency has in fact been encountered clinically in most, if not all, of these circumstances.

It was discovered early in the investigation of vitamin K that a number of the common bacteria, such as *E. coli*, *Staphylococcus aureus*, *B. subtilis*, the *Mycobacterium tuberculosis* synthesize the substance.⁹ Bacterial synthesis of vitamin K was further found to take place normally in the intestine of mammals and fowls, presumably distal to the mucosal areas in which absorption occurs. In the production of K-avitaminosis in chicks by dietary restriction, Almquist and Stokstad found it necessary to keep the chicks from access to their droppings, as otherwise deficiency did not develop.¹⁰ These points may be of significance in relation to the occurrence of hypoprothrombinemia in the newborn before the intestinal bacterial flora has been established, though the mechanism is not entirely clear.

Prothrombin deficiency is commonly present in obstructive jaundice, and in this condition poor absorption of vitamin K and impairment of hepatic synthetic power may be present in combination.¹¹ In a group of 50 cases of obstructive jaundice, which have come under the author's observation at the Massachusetts General Hospital, the plasma prothrombin concentration was invariably reduced before treatment, the average value in the cases of calculous obstruction being 65 per cent, and in the cases of carcinomatous obstruction 45 per cent. In every case, the prothrombin value improved after administration of vitamin K parenterally or vitamin K and bile salts orally, though the patients with calculous obstruction responded better, probably owing to greater hepatic functional reserve. In a group of 112 patients with obstructive jaundice operated upon at the Massachusetts General Hospital during the six-year period, 1931 to 1936 inclusive, 15 per cent died of massive postoperative hemorrhage. In the author's experience, the proper use of vitamin K before and after operation, together with adequate nutritional therapy, has entirely eliminated this hazard, even in patients with severe liver damage and initial prothrombin concentrations below 10 per cent.

It has been shown that an immediate postoperative reduction in plasma prothrombin concentration is the rule after operation for obstructive jaundice.^{12, 13, 14} The reduction may be as great as 30 or 40 per cent, and occurs most commonly within the first four days, from which the need for having the preoperative prothrombin value well above the hemorrhagic zone is apparent. The depression may follow spinal or local anesthesia, and probably is due to the hepatic trauma and blood loss of operation, as well as absence of prothrombin reserves. After operations for conditions other than obstructive jaundice, and in patients without liver disease, postoperative hypoprothrombinemia does not seem to occur.¹² In the early experiences with the clinical use of vitamin K, when only the crude alfalfa meal extracts and bile salts were available for oral treatment, the author observed two instances in which patients refused to take the material after operation for obstructive jaundice. The interesting point was that following the resultant massive wound hemorrhage a further reduction in plasma prothrombin concentration immediately

occurred, from which one is led to believe that hemorrhage may be a contributory factor in exhausting a depleted plasma prothrombin content

Prothrombin deficiency may occur in acute hepatitis, such as "catarrhal jaundice," though usually the reduction is moderate. The hypoprothrombinemia is not proportionate with the jaundice, and this gives the determination value in the differential diagnosis of jaundice from intrahepatic disease and from extrahepatic block. In the progression of acute hepatitis to acute yellow atrophy or liver failure, however, the plasma prothrombin concentration falls to values in the hemorrhagic range, which is below 40 per cent.¹⁶ Cirrhosis of the liver may be accompanied by moderate reduction in plasma prothrombin concentration, and in patients with bleeding esophageal varices the value may be less than 40 per cent. It is reasonable to suppose that in such cases the clotting defect may be a contributory factor and may lead to gross rather than microscopic bleeding from a lesion exposed to constant trauma.

Of special surgical interest is the group of cases in which toxic hepatitis, jaundice, and massive hemorrhage follow operation for peritoneal infections, such as perforative appendicitis, ruptured peptic ulcer, subdiaphragmatic abscess, and pelvic abscess. These complications seem to be more common when peritoneal sepsis is of gastro-intestinal origin, and determination of plasma prothrombin concentration as well as serum protein concentration should be routinely and periodically performed in the care of patients with such infection.¹⁵ The reduction in plasma prothrombin may develop rapidly and to an extreme degree. The resulting clotting defect may not only cause massive hemorrhage from operative wounds, but may retard inflammatory fixation and exudative confinement of the infection.

Reduction in plasma prothrombin concentration may be encountered during the administration of sulfanilamide, sulfapyridine and sulfathiazole in the treatment of infection. These drugs are known to exert a toxic effect on the liver, and presumably the hypoprothrombinemia comes from depression of liver function. Severe acute infections, however, may lead to reduction in plasma prothrombin concentration in the absence of chemotherapy, and the deficiency may be refractory to vitamin K treatment.¹⁶ Depression in plasma prothrombin has been observed to precede jaundice as an early indication of hepatitis in the chemotherapy of infections, and the determination should be freely used in the control of such therapy. At the same time the importance of nutritional measures directed at maintaining hepatic reserve, such as high carbohydrate and high vitamin intake and blood transfusions, during the management of chemotherapy is brought into focus.

Severe hypoprothrombinemia may develop in chronic external biliary fistula, if the patient does not take adequate amounts of bile salts orally in replacement. The author has seen near-fatal intracranial hemorrhage in two patients who failed to take the prescribed amount of bile salts and vitamin K following the surgical formation of external biliary fistula. The patients were middle-aged women without arteriosclerosis or hypertension, and in both

there was much reduction in hepatic reserve. The prothrombin concentration at the time of hemorrhage was below 10 per cent, and the bleeding was readily controlled by giving vitamin K parenterally. In a third case of complete external biliary fistula of 14 months' duration, there was unaccountable absence of the bleeding tendency and only moderate reduction in plasma prothrombin, even though the patient had had no dietary or replacement therapy. In this connection, it is worth remembering that the bile drained through an external fistula in the presence of liver damage, may have a low bile salt content, and hence may have little value in digestion and absorption. The cholic acid content of such bile should be determined, or else refeeding of the bile should not be practiced. In any event, cholic acid derivatives in capsule or tablet form are much more easily taken than a bacteria-laden, nauseating liquid.

Some doubt exists as to whether prothrombin deficiency can occur in man purely on the basis of insufficient intake of foods containing vitamin K. Scarborough concluded from a study of 18 patients showing outspoken evidence of scurvy, beriberi, or pellagra that the prothrombin values in the plasma were normal as determined by Quick's method.¹⁷ On the other hand, Kaik and Loznei,¹⁸ in studying four patients with clinical hypovitaminoses, found low plasma prothrombin values by a method of serial dilution of the unknown plasma with prepared prothrombin-free normal plasma. The question is rendered difficult by uncertainties as to liver function, bile salt excretion, and alterations in mucosal absorbing power in patients suffering from severe nutritional disturbances. In the author's experience, patients undergoing elective surgical operation and without clinical evidence of malnutrition frequently show moderately reduced plasma prothrombin values both by the method of Warner, Brinkhous, and Smith, and by Quick's method. For this reason normal control plasma must be selected with care. It remains to be shown, however, that a clinically significant degree of hypoprothrombinemia occurs in man purely from vitamin K lack.

Failure in absorption of vitamin K is to be expected in any condition in which the digestion and absorption of fat is seriously impaired.¹⁹ Idiopathic steatorrhea without evidence of liver disease may lead to spontaneous hemorrhage and hypocalcemic tetany from lack of vitamin K and vitamin D.²⁰ Prolonged hyperactivity of the intestine may result in prothrombin deficiency from poor absorption of vitamin K, as in chronic ulcerative colitis.^{28, 19, 21} Following parenteral injection of vitamin K in this condition, improvement in prothrombin concentration and diminution in bleeding from colonic ulcers has been observed.

There is abundant evidence now on record indicating the importance of prothrombin deficiency as a factor in hemorrhagic disease of the newborn.^{22, 7, 23, 24, 25} Brinkhous, Smith, and Warner observed a uniform reduction in the plasma prothrombin levels in the newborn and throughout infancy.²² During the first 11 days, values ranging from 26 to 44 per cent of normal were found, and thereafter there was a gradual rise until a nearly normal level was reached at the end of ten and one-half months. Maternal

prothrombin values, before and after delivery, were normal. As determined by Quick's method, plasma prothrombin in the newborn is apparently less commonly found reduced,²⁶ though prolongation of the prothrombin time can often be demonstrated from the first to the sixth day. The discrepancy in the findings by the two methods has led to the suggestion that the available prothrombin in the newborn has a higher "convertibility" than in the adult,²⁶ which would tend to compensate for the deficiency in the newborn. Mounting clinical evidence leaves no doubt as to the existence of profound hypoprothrombinemia in the newborn with hemorrhagic disease, and the response to the parenteral administration of vitamin K is dramatic and lifesaving. The rapidity of response suggests that the cause of the deficiency is lack of vitamin K rather than primary hepatic dysfunction, though the pathogenesis of the condition requires further study. Of similar significance is the finding that plasma prothrombin values in the newborn are much higher than average if the mother is given vitamin K before delivery, and this is true even if the maternal plasma prothrombin concentration is normal before the administration of vitamin K.²⁷

Hemorrhagic states into the etiology of which prothrombin-lack does not enter are thrombocytopenic purpura, hemorrhagic retinitis, aplastic anemia, leukemia, polycythemia vera, hemophilia, and multiple congenital telangiectases.²⁸⁻³⁰ In any case of bleeding of doubtful etiology, the prothrombin concentration of the plasma should be determined, but if the value is within normal limits no benefit is to be expected from vitamin K therapy.

Effects of Prothrombin Deficiency—It should be borne in mind that the extent of hemorrhage resulting from tissue trauma depends on the summation of opposing reactions. The cross-sectional area of the wound in the vascular bed, the size and contractility of the vessels laid open, the mobility and temperature of the part, the force of the blood pressure, and the richness of the local tissue thromboplastin supply are variables independent of the quality of the circulating blood, which, nevertheless, influence the success of the hemostatic process. From these considerations, it is clear that the clinical manifestations of prothrombin deficiency may be expected to vary greatly. Given absolute freedom from injury, no demand would be made on the hemostatic defenses, and complete absence of plasma prothrombin might pass unnoticed. The patient with obstructive jaundice and severely reduced plasma prothrombin concentration may get along without serious hemorrhage until surgical incision is made in the abdominal wall, as was repeatedly shown in clinical experience before the discovery of vitamin K. Likewise, the danger of hemorrhage from a lesion constantly exposed to trauma, such as duodenal ulcer, ulcers of chronic ulcerative colitis, and esophageal varices becomes greater as the clotting mechanism is crippled by lowering of plasma prothrombin concentration.

It is of interest to consider the reported sites of hemorrhage following operation in patients with obstructive jaundice treated before vitamin K was discovered. This is the group of patients in whom prothrombin deficiency is

most constant and severe, for a combination of etiologic factors is at work, such as lack of bile salts in the intestine, intrinsic liver damage, infection and, often, inadequate dietary intake. Bleeding into excoriated skin, nosebleeds, and bleeding from gums were not unusual. Severe postoperative bleeding, however, occurred into the wound, the gastro-intestinal tract, the peritoneal and pleural cavities, skeletal muscles, the urinary passages, and sometimes into the uterine canal. Hemoptysis and hemarthrosis were rare.

In a group of untreated patients with obstructive jaundice which came under the author's observation during the past three years, tests for blood in the stools were frequently positive. In nine of 22 patients with calculous obstruction of the common duct, and in 13 of 22 with neoplastic obstruction the guaiac test on the stools was strongly positive, and the test became negative under vitamin K therapy before operation, coincident with improvement in plasma prothrombin concentration. No ulcerations were visible in roentgenologic studies of the gastro-intestinal tract, so one is led to suppose that the bleeding was from small excoriations of the mucosa.

Petechial hemorrhage is uncommon in prothrombin deficiency, though small hemorrhages into cutaneous abrasions produced by scratching are frequently present in patients with obstructive jaundice. Numerous and large ecchymotic areas were observed over the trunk in a patient with idiopathic steatorrhea and plasma prothrombin values below 15 per cent. Epistaxis and bleeding from the gums may occur in prothrombin-lack. Reference has already been made to two patients with chronic external biliary fistula who had severe intracranial hemorrhages as a result of neglecting bile salt and vitamin K therapy. The author has seen hemoptysis from lung abscess and uterine hemorrhage from hyperplastic endometritis associated with plasma prothrombin concentrations of 65 to 75 per cent, but the importance of the hypoprothrombinemia in such cases is open to question. A group of 30 patients with chronic pulmonary tuberculosis were found to have moderate hypoprothrombinemia, but the values were no lower in the patients having hemoptysis. Bleeding into the urinary tract is rare in prothrombin-lack in the absence of adequate local causes, but such clotting deficiency may perhaps occasionally be a contributory factor.

A consideration, possibly of great importance, is the rôle of plasma prothrombin in resistance to infection. The thrombosis of lymphatics and capillaries at the boundary of an inflammatory process and the coagulation of plasma exudate in the region presumably would be impaired by prothrombin deficiency, although the direct conversion of fibrinogen into fibrin by bacterial or inflammatory products might operate in compensation. When large blood vessels become involved in advancing necrotizing infections, the rapid formation and organization of a firm thrombus in response to endo-arteritis is of lifesaving importance.

The characteristic peritoneal reaction to trauma is capillary dilatation and transudation of plasma, with the formation of a plastic exudate. The surgeon's suture line after gastro-intestinal operation is quickly sealed over in this

manner, thus initiating fibroblastic healing, and at the same time preventing bacterial leakage. The efficiency of this reaction, on which the safety of abdominal surgery depends, probably is influenced by various factors, but of unquestionable importance is the plasma content of prothrombin and fibrinogen. The formation of excessive peritoneal adhesions after peritoneal trauma may arise in factors which exaggerate this vital protective process.

Hyperprothrombinemia—The possible occurrence of hyperprothrombinemia, either spontaneously or in response to vitamin K therapy, has been subjected to study. In examining normal individuals and a large number of patients with a variety of diseases, the author has seen only three instances in which the plasma prothrombin concentration, as determined by a slightly modified two-stage method,²⁸ was above 110 per cent. In one of these patients dehydration was present, as evidenced by elevated plasma protein concentration, and this was adequate explanation for the hyperprothrombinemia. The other two patients were afflicted with a tendency to recurrent thromboses of peripheral veins without any satisfactory explanation. It is possible that in the latter patients a hyperactive clotting mechanism was of pathologic importance. There appears to be no danger of producing hyperprothrombinemia from administering excess of vitamin K and, of course, it is generally true of vitamin therapy that many times the effective dose can be taken without harm. The author has given convalescent surgical patients with normal prothrombin values up to ten times the effective oral dose of vitamin K without ill effects and without elevating the plasma prothrombin concentration above 100 per cent.

Prothrombin Determination as a Liver Function Test—Since plasma prothrombin is formed chiefly if not entirely in the liver, it is not surprising that factors interfering with hepatic function result in depression of the plasma prothrombin concentration. Experimental and clinical evidence indicates that reduction in the prothrombin value may be an early and sensitive index of decline in hepatic reserve.²⁹ After chloroform anesthesia in patients or in animals, the first detectable sign of the hepatotoxic action of the drug is a sharp reduction in plasma prothrombin concentration.^{14, 3} In patients with hypoprothrombinemia, the improvement in the prothrombin value following a single adequate dose of water-soluble vitamin K given parenterally may be used as a liver function test.³⁰ In patients with liver failure and prothrombin deficiency massive doses of vitamin K given parenterally or orally with bile salts may be without benefit, though complete absence of response indicates extremely severe hepatic change.¹⁶ Intercurrent infection such as pneumonia or cholangitis, may produce immediate lowering of plasma prothrombin concentration in a patient receiving a daily adequate dosage of vitamin K.^{11, 12} The lability of plasma prothrombin concentration makes it important to determine the value frequently and regularly in the management of cases of obstructive jaundice.

Treatment of Prothrombin Deficiency—Before the isolation and identification of the chemical nature of vitamin K in 1939, only crude extracts obtained

from spinach, alfalfa meal, putrefied fish meal, *etc*, were available for use in treatment. The crude extract was given orally with bile salts, and the efficacy of the therapy is attested to by many clinical and experimental data. Through the efforts of Dam,^{31, 32} Almquist,^{33, 34, 35} Doisy and his colleagues,^{36, 37} Fieser^{38, 39} and others, a number of 1,4-naphthoquinone derivatives have been shown to have high vitamin K potency when given in chemically pure form. Vitamin K activity is found in various naturally occurring mono- or di-alkyl 1,4-naphthoquinone compounds, including vitamin K₁ derived from spinach and vitamin K₂ from putrefying fish meal. One of the most potent vitamin K substances studied to date is 2-methyl-1, 4-naphthoquinone, and there is a growing tendency to express the value of other materials in terms of this substance, rather than in the uncertain and variable units proposed earlier by different investigators.

The known naturally occurring vitamin K substances are fat-soluble, and clinical needs led to a search for water-soluble substances which could be more easily administered. A number of water-soluble, highly potent compounds have been identified, as recently described by Fieser, Tishler, and Sampson.³⁹ These substances can be injected in aqueous solution, or they can be given orally, and they are absorbed from the gastro-intestinal tract in the absence of bile salts.^{40, 41} All the known fat-soluble and water-soluble compounds with vitamin K activity have low toxicity, as shown by extensive studies on small animals and in the clinic.

The following methods are available in the administration of vitamin K to patients:

- (1) Crude extracts may be given by mouth, together with bile salts.
- (2) Synthetic fat-soluble vitamin K (2-methyl-1,4-naphthoquinone) may be given by mouth together with bile salts.
- (3) Synthetic fat-soluble vitamin K in oil may be sterilized and injected intramuscularly.
- (4) Synthetic water-soluble vitamin K may be administered by mouth.
- (5) Synthetic water-soluble vitamin K may be sterilized and injected subcutaneously, intramuscularly, or intravenously.

In most instances where the fat-soluble synthetic preparation or the crude extracts are given by mouth, bile salts also should be administered, for even in the absence of jaundice the absorption of the fat-soluble material from the intestines may be facilitated by additional quantities of bile salts.¹⁶ An adequate daily dose is 2 to 4 mg. of 2-methyl-1,4-naphthoquinone or an equivalent amount of one of the other preparations, and it has been found that much larger doses are of no avail if no improvement in the prothrombin concentration follows doses of this size. If bile salts are also being given 1 to 2 Gm. per day is sufficient. In patients with severe liver damage, the author prefers to give vitamin K parenterally and avoid the administration of bile salts. In urgent need, as in the presence of active hemorrhage, vitamin K should be administered parenterally, and the response occurs within a few hours. For patients

who are vomiting, or in whom uncertainty as to absorption exists, the parenteral route should be used

In the author's experience, hypoprothrombinemia refractory to vitamin K treatment may be encountered in two groups of patients. As already noted, liver function may be reduced to such a point that vitamin K is not properly utilized no matter how generous the supply, or how it is administered^{16, 45, 46}. There is also a group of patients with chronic, severe sepsis, such as pyelonephritis, osteomyelitis, or subdiaphragmatic abscess, in whom prothrombin deficiency of moderate degree may exist, and in these patients the deficiency may not respond to vitamin K therapy. In such conditions, blood transfusions are in order, and fresh rather than "bank" blood should be used^{42, 43}. The average blood transfusion of 500 cc may be expected to effect a transitory rise in the adult patient's plasma prothrombin concentration of about 10 per cent^{26, 12}.

Since the formation of plasma prothrombin is a function of the liver, it should be borne in mind that an essential part of treatment of prothrombin deficiency consists in the measures known to influence liver function favorably⁴⁴. A high intake of carbohydrate and the proper kind of protein is important, as well as a high vitamin intake. The fluid and electrolyte needs of the patient must be carefully met. In connection with surgical operation, the proper choice of time and anesthesia, and the division of the necessary surgical trauma by two-stage procedures in certain cases are matters for careful consideration, if depleted hepatic reserve is not to be totally overtaxed.

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THE TREATMENT OF FRACTURES OF THE HUMERUS BY MEANS OF A HANGING PLASTER CASE—"HANGING CAST"*

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SINCE 1935, the majority of fractures of the neck and shaft of the humerus have been treated routinely on the Bone and Joint Service of Receiving Hospital by the hanging plaster case

This encasement was first advocated by Dr J A Caldwell in 1933 for treatment of some fractures of the shaft of the humerus

The hanging plaster case consists, simply, of a circular plaster bandage which encases the upper extremity from its upper third to the wrist, it holds the elbow in 90° flexion, and is suspended from the neck by a sling

The plaster bandage is applied with the patient either sitting or recumbent as convenient or as condition of the patient permits, the elbow flexed to a right angle, with the forearm held in midpronation. An adequate length of stockinette is pulled over the arm, and a strip of saddlers' felt, one inch in width, is made to encircle the wrist just above the ulnar styloid. The plaster bandage is applied either with no other padding or with a few turns of flannel bandage

For adults, four rolls of plaster, four inches by six yards, are used, while three rolls are used for children

A loop for a sling is made just above the wrist on the upper surface of the encasement by a few turns of the last bandage applied. This loop can be applied either slightly medialward or lateralward to the midline of the upper surface of the encasement to help correct inward or outward angulation of the lower fragment (Fig 1)

Lateral angulation can be readily corrected by a wedge made of felt, plaster, sponge rubber, or sheet cotton covered with plaster, placed on the inner side of the elbow (Fig 2). In some cases of fractures of the humeral neck with medial bowing, we have found a roll of sponge rubber, two and one-half inches in diameter, placed high in the axilla and fixed to the encasement, very effective in correcting this deformity (Fig 3)

The plaster bandage is usually applied after roentgenologic examination. However, when the patient's general condition is not good, or the fragments are found to be in an unsatisfactory position for this method of treatment, these difficulties are first rectified before the encasement is applied

The patient is instructed after application of the hanging plaster case to allow the arm to swing freely at his side at all times. Many patients have an inclination to rest the elbow on the arm of a chair or some convenient object when sitting. This is contrary to the main purpose of the encasement

* Since submitting this article we have the results on an additional seventy-six cases which, including those described in an earlier issue elsewhere, make a total of two hundred and fifty-three cases treated in the Bone and Joint Department of the Receiving Hospital, Detroit, Michigan

which is traction by gravity. This difficulty is greatly lessened when the patient is made to realize the principle of this method of treatment, and that



FIG 1—The hanging case showing suspension loop

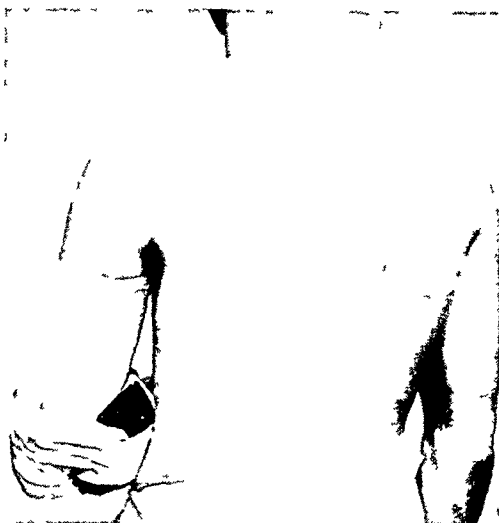


FIG 2—Showing the sponge rubber roll in position, in order to correct lateral angulation

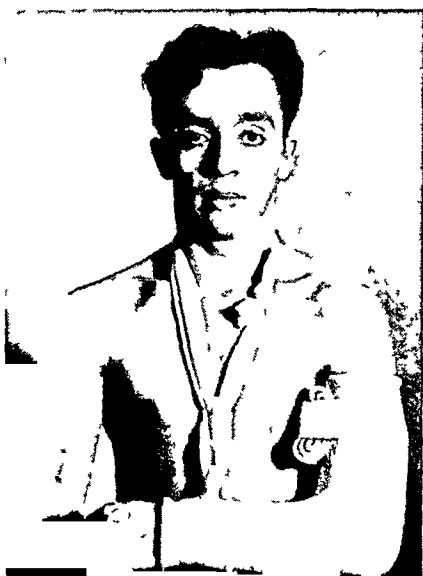


FIG 3—Showing the felt roll in position in order to correct medial displacement of the lower fragment

his chances for a good result depend wholly on his full cooperation.

Some patients find it more comfortable to sleep sitting in a chair for the first week or so, others use a back rest which permits the arm to swing as free as when in the erect position. The remainder sleep satisfactorily with upper arm either resting on a pillow or with the whole arm placed across the chest.

Active motion of the wrist and hand has been encouraged from the beginning. The patient is instructed to lean forward and let the shoulder swing in circular motions several times a day. These passive movements are sufficient to preserve considerable free motion at the shoulder joint until active motion can be safely instituted. After a few days active motion is allowed in the anteroposterior plane. Whenever moderate callus formation can be demon-

strated roentgenologically, active abduction is encouraged.

Roentgenograms are taken two or three days after application of the encasement to determine the position of the fragments, and if necessary, adjustments are then made. From then on until union is adequate to allow removal of the encasement, check-up roentgenograms are taken at two-week intervals.

Fractures of the humerus considered unsuitable for treatment by the hanging plaster case are those that involve the condyles or supracondylar area, badly comminuted fractures of the head with poor position of the fragments, those of the head and neck associated with dislocation at the shoulder joint, and fractures of the greater tuberosity with displacement. These are treated by other methods and none are included in this series.

Since the first report of the results obtained in 58 cases treated by the hanging plaster case in Receiving Hospital by the senior author and Dr. M. G. Rosenbaum, in 1937, the final results of 119 additional cases of the Bone and Joint Service have been observed. This brings the total number of cases, followed from the time they were first seen in the clinic to their discharge, up to 177.

This, however, does not include all cases of the Bone and Joint Service that were treated by this method. Many of these patients failed to return to the clinic for check-up examinations, a number were transferred to other hospitals, or discharged to the care of their family physician, consequently, making it impossible for us to check the end-results.

For uniformity in recording results, the same classification of fractures and terms used to describe the final results obtained in the 58 cases of the first report are again used. This classification is based upon the roentgenographic findings of the injury when first seen: (1) Fractures of the upper third of the humerus—(a) in good or fair position, (b) in poor position; (2) Fractures of the middle and lower thirds of the humerus—(a) in good or fair position, (b) in poor position.

The final results of shoulder function procured upon removal of the encasement or discontinuance of physiotherapy were designated by the terms "excellent," "good," "fair," and "poor." "Excellent" denotes a shoulder which functions almost as well as before injury. Active shoulder abduction to 90° with only slight limitation of external rotation is termed "good." A less degree of function is "fair." "Poor" indicates only slight motion.

There were 49 fractures of the upper third of the humerus in good or fair position (Table I). Of these, the youngest patient was seven years of age and the oldest 85. Hanging plaster encasements were applied in all cases in this group without any previous manipulation. In all, except four cases (Cases 4, 8, 12, and 34) the encasements were put on from a few hours to five days following the injury (Figs. 4 and 5).

Case 4 suffered from a head injury received at the time of the arm injury. She remained in bed for two weeks with the injured arm strapped to her side while convalescing from the skull injury.

Cases 8 and 12 were compound fractures. Case 8 remained in bed for the first five days with the arm in skin traction and a Thomas arm splint. Case 12 was complicated by an injury to the radial nerve and severe hemorrhage. A Kirschner wire was inserted through the olecranon from which a five-pound weight was suspended for the first 16 days.

TABLE I

SUMMARY OF FRACTURES OF THE UPPER THIRD OF THE HUMERUS INCLUDING THE SURGICAL NECK—
IN GOOD OR FAIR POSITION

Case No	Age	Sex	Type of Fracture	Date of Injury	Encase- ment Applied	Number of Weeks in En- casement	Final X ray	Physio- therapy	Function of Shoulder
1 A B	70	F	Oblique	1- 2-37	1- 2-37	7	Excellent	For 4 wks	Excellent
2 E S	57	F	Irregular transverse	1-14-37	1-14-37	6	Excellent	No	Excellent
3 J T	67	F	Oblique comminuted	1-23-37	1-23-37	6	Good	No	Excellent
4 I J	70	F	Irregular oblique	2- 1-37	2-15-37	6	Good	No	Good
5 R L	45	M	Oblique	2- 1-37	2- 1-37	4	Excellent	No	Excellent
6 A B	54	M	Oblique	2- 5-37	2- 6-37	5	Excellent	No	Excellent
7 J P	44	M	Transverse	2- 5-37	2- 5-37	6	Excellent	No	Excellent
8 H C	27	M	Spiral comminuted	2- 6-37	2-11-37	6	Excellent	No	Excellent
9 M K	16	F	Transverse	2-13-37	2-16-37	5	Excellent	No	Excellent
10 L C	32	F	Oblique	2-22-37	2-25-37	6	Excellent	No	Excellent
11 J H	10	M	Irregular transverse	3-13-37	3-13-37	5	Good	No	Excellent
12 C K	58	F	Oblique comminuted	4- 8-37	4-24-37	4	Good	No	Good
13 M J	45	F	Oblique	4- 9-37	4- 9-37	7	Excellent	For 2 wks	Excellent
14 V M	52	F	Oblique comminuted	5- 3-37	5- 3-37	6	Excellent	For 1 mo	Good
15 D B	9	F	Oblique	5- 6-37	5- 6-37	5	Excellent	No	Normal
16 M O	60	F	Transverse	5-31-37	6- 1-37	7	Excellent	No	Excellent
17 V H	40	M	Spiral oblique	6-13-37	6-15-37	5	Good	No	Good
18 M B	68	M	Transverse	7- 9-37	7- 9-37	4	Excellent	No	Excellent
19 A M	79	F	Irregular transverse	7-26-37	7-26-37	7	Fair	No	Good
20 R R	82	M	Oblique	8-21-37	8-22-37	8	Excellent	No	Excellent
21 J S	7	M	Transverse	9-15-37	9-15-37	5	Excellent	No	Normal
22 J R	60	M	Oblique	9-22-37	9-22-37	7	Excellent	No	Excellent
23 A J	21	M	Oblique comminuted	2-27-38	3- 1-38	9	Excellent	No	Excellent
24 I J	60	M	Irregular transverse	4-19-37	4-19-37	6	Excellent	No	Excellent
25 H C	64	M	Oblique	5-14-38	5-14-38	6	Excellent	No	Excellent
26 W Y	66	M	Spiral oblique	7-19-38	7-19-38	12	Excellent	No	Good
27 R M	15	F	Oblique	8-10-38	8-10-38	4	Excellent	No	Normal
28 M B	47	F	Oblique	10- 7-38	10- 7-38	8	Excellent	For 2 wks	Excellent
29 G S	61	M	Transverse	12- 5-38	12- 5-38	6	Excellent	No	Excellent
30 M D	53	M	Oblique	12-24-38	12-24-38	6	Excellent	No	Excellent
31 L R	47	M	Oblique	1-14-39	1-14-39	5	Good	No	Excellent
32 S B	68	F	Oblique	2-17-39	2-17-39	5	Excellent	No	Excellent
33 M R	55	F	Transverse	2-17-39	2-18-39	4	Excellent	For 2 wks	Excellent
34 J S	67	M	Irregular oblique	3-18-39	3-24-39	5	Excellent	No	Excellent
35 J L	43	M	Transverse comminuted	3-19-39	3-19-39	7	Good	No	Fair
36 G B	13	M	Epiphyseal separation	5-13-39	5-13-39	4	Excellent	No	Excellent
37 A R	8	M	Transverse	5-27-39	5-27-39	5	Excellent	No	Excellent
38 C M	35	F	Transverse impacted	6-17-39	6-17-39	7	Excellent	No	Excellent
39 D M	15	M	Oblique	6-24-39	6-24-39	6	Excellent	No	Excellent
40 F K	67	M	Oblique comminuted	7- 5-39	7- 5-39	10	Good	No	Good
41 M P	10	F	Transverse	7- 8-39	7- 8-39	5	Excellent	No	Excellent
42 J L	70	M	Oblique	7-25-39	7-26-39	6	Excellent	No	Excellent
43 L S	39	F	Oblique comminuted	8-26-39	8-29-39	7	Excellent	No	Excellent
44 M W	37	M	Shattering	9- 3-39	9- 3-39	14	Excellent	No	Good
45 J P	31	M	Oblique comminuted	9-11-39	9-11-39	9	Excellent	No	Excellent
46 S M	15	M	Oblique	9-26-39	9-26-39	5	Excellent	No	Excellent
47 W H	36	M	Oblique	10-13-39	10-14-39	5	Excellent	No	Excellent
48 C H	11	F	Oblique	12-13-39	12-13-39	6	Excellent	No	Excellent
49 D E	85	F	Oblique	1- 6-40	1- 6-40	7	Excellent	No	Excellent

TABLE II

SUMMARY OF FRACTURES OF THE UPPER THIRD OF THE HUMERUS INCLUDING THE SURGICAL NECK—IN POOR POSITION

Case No	Age	Sex	Date of Injury	Type of Displacement	Corrective Procedure	Number of Weeks in Encasement	Final X-ray	Physiotherapy For 2 wks	Function of Shoulder
50 J Q	61	M	1-12-37	Shaft medial to head with $\frac{1}{2}$ inch overriding	Hanging cast for 2 wks then open reduction and shoulder specia, with arm in abduction for 3 wks "hanging cast"	7	Poor	For 2 wks	Poor
51 I S	50	F	2-4-37	Shaft displaced mediallyward	Manipulation, "hanging cast"	7	Good	No	Excellent
52 A T	10	F	3-1-37	$\frac{1}{2}$ inch overriding lateral apposition	Hanging cast	6	Excellent	No	Excellent
53 J H	51	M	3-10-37	Outward bowing with $\frac{1}{4}$ inch overriding	Hanging cast	8	Excellent	For 2 wks	Excellent
54 B S	79	F	4-2-37	$\frac{1}{2}$ inch medial displacement	Manipulation, "hanging cast"	5	Excellent	No	Excellent
55 A J	66	M	4-21-37	$\frac{1}{4}$ inch overriding shaft lateral to head	"Hanging cast"	5	Excellent	No	Excellent
56 H W	32	M	6-2-37	Lateral angulation not in apposition	"Hanging cast"	6	Excellent	No	Excellent
57 K O	5	F	7-8-37	Shaft medial to head	"Hanging cast"	5	Excellent	No	Excellent
58 J G	45	M	7-24-37	Shaft lateral to head	"Hanging cast"	5	Excellent	No	Excellent
59 L G	12	M	8-18-37	Shaft medial to head $\frac{1}{4}$ inch overriding	"Hanging cast"	5	Excellent	No	Excellent
60 M L	43	M	10-16-37	$\frac{1}{2}$ inch overriding lateral separation	"Hanging cast"	5	Good	No	Excellent
61 W F	57	M	1-1-38	$\frac{1}{2}$ inch overriding, lower fragment medial to upper	"Hanging cast"	5	Good	No	Excellent
62 F W	70	F	4-5-38	Shaft lateral to head	Manipulation, "hanging cast"	6	Good	No	Good
63 F O	42	M	4-9-38	Lateral apposition rotation of head	Manipulation, "hanging cast"	5	Good	No	Excellent
64 G H	75	M	5-6-38	Anterior and medial displacement of shaft, marked rotation of head	Skeletal traction for two weeks then open reduction and 90° abduction in encasement for three weeks, "hanging cast"	3	Good	No	Fair
65 C L	49	M	7-24-38	Marked lateral angulation and lateral separation	"Hanging cast"	6	Good	No	Excellent
66 L B	60	M	4-2-39	Shaft medial to head head rotated	Manipulation, "hanging cast"	6	Fair	No	Good
67 B P	55	M	3-23-39	Impacted considerable lateral angulation	Manipulation and "hanging cast" for two weeks, then skin traction following a second manipulation for two weeks then "hanging cast"	6	Fair	No	Good
68 M G	29	M	7-23-39	$\frac{1}{2}$ inch overriding	"Hanging cast"	6	Excellent	No	Excellent
69 M D	51	M	11-1-39	Shaft medial to head	Manipulation, "hanging cast" with sponge rubber pad in axilla	7	Excellent	For 2 wks	Excellent
70 M P	34	F	12-4-39	Shaft medial to head $\frac{1}{2}$ inch overriding	"Hanging cast, "sponge rubber pad in axilla"	6	Excellent	No	Excellent
71 F F	71	M	1-12-40	Shaft displaced medially	"Hanging cast, "sponge rubber pad in axilla"	8	Excellent	For 2 wks	Excellent
72 I W	43	M	1-24-40	Shaft displaced medially	"Hanging cast, "sponge rubber pad in axilla"	7	Excellent	No	Excellent



FIG 4—Roentgenogram of a fracture of the surgical neck of the humerus before application of the hanging case



FIG 5—Roentgenogram of the same patient shown in Figure 4 two days after the application of the hanging case

Case 34 suffered from delirium tremens which necessitated restraining the patient in bed for eight days. During this time the fractured arm was strapped to his side.

Five of the 49 patients in Group I had compound fractures (Cases 8, 12, 23, 44 and 45). All were gunshot wounds except Case 12. Case 35 was a fracture through a bone cyst in the upper third of the shaft of the humerus. Healing of the fracture did not result in the disappearance of the cyst.

The length of time that the encasement was left on in this group ranged from 4 to 14 weeks, the average time being about six and one-half weeks. Union was prompt in all fractures except Case 44. This had a badly shattered fracture caused by a gunshot wound, which required 14 weeks before union became sufficient to permit removal of the encasement.

Excellent function of the shoulder was obtained in 40 cases. Eight patients obtained only 90° shoulder abduction. One patient (Case 35) was very uncooperative from the beginning, and persistently removed the sling from his neck and carried the arm buttoned inside his shirt. When last seen three months after removal of his encasement, he had only 60° shoulder abduction. This probably could have been improved by physiotherapy, but the patient refused treatment.

Table II summarizes the study of 23 fractures of the upper third of the humerus which were in poor position as shown roentgenologically. The youngest age was age 10, and the oldest 76. In many the deformity was apparent on physical examination. In 11 cases the shaft was displaced

TABLE III

SUMMARY OF FRACTURES OF THE MIDDLE AND LOWER THIRD OF THE HUMERUS—IN GOOD OR FAIR POSITION

Case No	Age	Sex	Type of Fracture	Date of Injury	Encasement Applied	Number of Weeks in Encasement	Final X-ray	Physiotherapy For 2 wks	Function of Elbow and Shoulder	Cosmetic Result
73 R B	8	M	Transverse middle third	1-16-37	1-18-37	6	Excellent	No	Normal	Excellent
74 J M	12	M	Irregular transverse middle third	4-26-37	4-27-37	7	Good	No	Excellent	Excellent
75 K S	21	F	Oblique comminuted middle and lower third	5-17-37	5-18-37	8	Excellent	No	Normal	Excellent
76 A N	59	M	Oblique middle third	5-18-37	5-18-37	5	Excellent	No	Normal	Excellent
77 S G	30	M	Oblique middle third	6-20-37	6-22-37	5	Excellent	No	Normal	Excellent
78 A W	43	F	Spiral oblique lower and middle third	6-20-37	6-21-37	6	Excellent	No	Normal	Excellent
79 A C	11	M	Transverse middle third	9-11-37	9-11-37	5	Excellent	No	Normal	Excellent
80 B P	28	F	Irregular oblique middle third	9-21-37	9-25-37	5	Excellent	No	Normal	Excellent
81 M 1	45	M	Irregular transverse middle third	3-5-38	3-8-38	8	Excellent	No	Normal	Excellent
82 J G	45	M	Oblique lower and middle third	4-11-38	4-20-38	5	Excellent	No	Normal	Excellent
83 C R	47	M	Oblique lower and middle third, eight months old with nonunion	12-25-37	8-20-38	10	Excellent	No	Good	Excellent
84 E S	15	M	Transverse middle third	10-11-38	10-25-38	5	Excellent	No	Excellent	Excellent
85 R C	17	M	Shattering (gunshot) lower and middle third	1-17-39	2-8-39	5	Excellent	For 6 wks	Excellent	Excellent
86 J S	28	F	Irregular transverse, middle third	2-7-39	2-8-39	7	Excellent	No	Excellent	Excellent
87 L T	54	M	Oblique middle third	7-1-39	7-1-39	8	Excellent	No	Normal	Excellent
88 J V	66	M	Oblique middle third	12-15-39	12-15-39	6	Excellent	No	Normal	Excellent
89 A F	13	F	Transverse middle third	12-22-39	12-23-39	6	Excellent	No	Normal	Excellent
90 S M	40	M	Oblique middle third	1-27-40	1-27-40	5	Excellent	No	Normal	Excellent
91 A A	24	F	Oblique lower and middle third	2-16-40	2-16-40	6	Excellent	No	Normal	Excellent

medially to the head, four of these were overriding. Four had the shafts displaced laterally, while in two cases the humeral head was markedly rotated.

Thirteen patients had encasements applied without any previous attempt at reduction. In three of these cases, a sponge rubber roll, placed high in the axilla, corrected the medial displacement of the shaft. Seven were successfully reduced before application of the encasement by manipulation under fluoroscopic control. Two had general anesthesia, while one had a local anesthetic, four were seen early and were manipulated without anesthesia.

In Case 67, impaction was broken up, and lateral angulation corrected under general anesthesia. A check-up roentgenogram, taken two weeks later, showed the humeral shaft to be displaced medialward. The hanging plaster case was then removed, and the fracture reduced by a second manipulation under general anesthesia. Reduction was successfully maintained by skin traction to the upper arm, with the elbow flexed to 90°. Traction was discontinued after two weeks and a second encasement was applied.

In this group, exclusive of those fractures that were treated by open reduction or by traction before application of the encasement, an average period of six weeks was spent in the plaster case.

Excellent shoulder function was obtained in 18 cases. Three cases had limitation of shoulder abduction to 90°. Cases 50 and 64, which had open reductions, obtained 60° and 80° abduction, respectively. Physiotherapy for two weeks in Case 50 did not effect any improvement.

Table III summarizes the data of 19 patients who sustained fractures of the middle and lower thirds of the humerus, with little or no displacement. Their ages varied from eight to 66 years.

Plaster encasements were applied over a period ranging from a few hours to four days following injury, except in four cases (Cases 82, 83, 84, and 85). Manipulative and other corrective procedures were not necessary.

Delirium tremens in Case 82 caused a nine-day delay in application of the encasement. Case 83, when admitted to the hospital, had a delayed union of a fracture sustained approximately eight months previously. This patient, affected by a mental derangement, was deemed a poor operative risk. However, after ten weeks' treatment in a hanging plaster case union was solid.

Case 84 had a skull fracture in addition to the humeral fracture. He was placed in skin traction for 14 days, followed by the hanging plaster case.

Case 85 was a gunshot wound. After debridement and closure, skeletal traction through the olecranon was applied. After three weeks skeletal traction was discontinued and the arm treated with a hanging plaster case.

The average length of time of treatment with the hanging case in this group, exclusive of those in which there was delay of more than four days before application of the encasement, was approximately six weeks.

Uniformly, excellent functional and cosmetic results were obtained in this group. Only one patient had limitation of motion, and this fracture, as

TABLE IV

SUMMARY OF FRACTURES OF THE MIDDLE AND LOWER THIRD OF THE SHAFT OF THE HUMERUS—IN POOR POSITION

Case No	Age	Sex	Date of Injury	Type of Fracture	Corrective Procedure	Number of Weeks in Encasement	Final X-ray	Physiotherapy	Function of Elbow and Shoulder	Cosmetic Result
92 L B	45	F	1-23-37	Transverse $\frac{1}{2}$ inch overriding	Manipulation under general anesthesia, hanging cast	9	Excellent	No	Excellent	Excellent
93 E W	50	F	1-23-37	Transverse $\frac{1}{2}$ inch overriding anterior bowing	Hanging cast	5	Excellent	For 2 wks	Normal	Excellent
94 G W	64	M	3-3-37	Transverse $\frac{1}{2}$ inch overriding marked anterior angulation	Hanging cast	10	Good	For 2 wks	Normal	Excellent
95 A H	14	F	3-6-37	Oblique $\frac{1}{2}$ inch overriding	Manipulation without anesthesia, hanging cast	6	Excellent	No	Normal	Excellent
96 N C	44	M	3-28-37	Oblique $\frac{1}{4}$ inch overriding	Hanging cast	6	Excellent	No	Normal	Excellent
97 A K	52	M	5-27-37	Irregular transverse $\frac{1}{4}$ inch overriding	Hanging cast	9	Excellent	For 2 wks	Excellent	Excellent
98 A J	43	M	6-5-37	Oblique comminuted marked anterior bowing	Hanging cast	10	Excellent	No	Good	Excellent
99 R M	10	M	6-5-37	Transverse $\frac{3}{4}$ inch overriding comminuted	Hanging cast	5	Excellent	No	Excellent	Excellent
100 S M	8	F	6-15-37	Oblique $\frac{1}{2}$ inch overriding	Hanging cast	5	Excellent	No	Excellent	Excellent
101 A D	39	M	7-2-37	Transverse $1\frac{1}{2}$ inches overriding	Hanging cast	9	Good	For 2 wks	Good	Excellent
102 F L	16	M	7-27-37	Oblique lateral separation of fragments	Hanging cast	7	Good	No	Good	Excellent
103 P L	13	M	8-8-37	Oblique anterior and lateral displacement of lower fragment	Hanging cast	5	Good	No	Excellent	Excellent
104 O F	33	M	8-6-37	Transverse $\frac{1}{2}$ inch overriding	Manipulation, hanging cast	4	Good	No	Excellent	Excellent
105 A C	21	M	12-2-37	Spiral oblique $\frac{1}{2}$ inch overriding	Hanging cast	6	Excellent	No	Normal	Excellent
106 S K	34	F	2-5-38	Oblique $\frac{1}{2}$ inch overriding	Manipulation without anesthesia, hanging cast	7	Good	No	Excellent	Excellent
107 A W	82	F	3-9-38	Spiral oblique 1 inch overriding	Hanging cast	9	Good	No	Excellent	Excellent
108 P M	23	F	3-27-38	Oblique comminuted 1 inch overriding	Skin traction for 4 weeks, hanging cast	8	Good	No	Excellent	Excellent
109 W C	53	M	5-8-38	Irregular oblique 1 inch overriding	Attempted reduction by manipulation under general anesthesia skeletal traction for 2 weeks, hanging cast	5	Good	No	Excellent	Excellent
110 W B	13	M	7-22-38	Oblique $\frac{3}{4}$ inch overriding	Skin traction for 1 week, hanging cast	8	Excellent	No	Normal	Excellent
111 M G	40	M	7-29-38	Oblique $\frac{1}{4}$ inch overriding	Hanging cast	9	Good	No	Excellent	Excellent
112 R M	86	M	8-12-38	Spiral oblique comminuted lateral separation of fragments anterior bowing	Hanging cast	7	Excellent	No	Excellent	Excellent
113 V B	22	M	11-23-38	Oblique comminuted anterior bowing	Hanging cast	6	Excellent	No	Normal	Excellent
114 T H	32	M	12-30-38	Oblique 1 inch overriding	Hanging cast	8	Good	No	Normal	Excellent
115 H S	65	M	1-13-39	Oblique 1 inch overriding	Skeletal traction for 3 weeks, hanging cast	6	Excellent	No	Excellent	Excellent
116 G R	79	M	5-3-39	Oblique $\frac{1}{2}$ inch overriding	Hanging cast	7	Excellent	No	Normal	Excellent
117 R C	22	M	7-4-39	Oblique comminuted $\frac{1}{2}$ inch overriding	Hanging cast	6	Excellent	No	Normal	Excellent
118 L D	23	M	10-20-39	Oblique comminuted 1 inch overriding	Hanging cast	5	Excellent	No	Normal	Excellent
119 J V	38	M	2-13-40	Oblique lateral apposition anterior bowing	Hanging cast	6	Excellent	No	Normal	Excellent



FIG 6—Roentgenogram of a fracture of the middle third of the humerus



FIG 8—Roentgenogram of a fracture of the lower third of the humerus

previously reported, had been an eight-month delayed union before coming under observation. However, 90° active abduction and 75° external rotation had been obtained.

Table IV summarizes 27 fractures involving the middle and lower third of the shaft of the humerus in poor apposition and alignment, the patients ranging in age from eight to 86 years. Twenty-two of these fractures were overriding, three laterally separated, without overriding, and two were badly comminuted with marked anterior bowing (Figs 6, 7, 8 and 9).

In 19 instances no corrective procedures other than application of the hanging plaster case were used. Three others were successfully reduced by manipulation without the aid of anesthesia, while one required a general anesthetic. An attempted manipulation under general anesthesia resulted in failure in one instance. For two weeks, this patient was placed in skeletal traction which brought the fragments into position and maintained them there.

The remaining three patients were previously treated by traction, one by skeletal traction for three weeks, and the other two by skin traction for two and three weeks, respectively.

This group of patients required a slightly longer period in the encasement than the other three groups. The average length was approximately seven weeks.

The end-results for function of the shoulder in 25 cases were excellent. Two had only slight limitation of motion. Cosmetic results were excellent in all.

SUMMARY

(1) Since 1935, the majority of fractures of the neck and shaft of the humerus have been successfully treated on the Bone and Joint Service of Receiving Hospital by the hanging plaster case.

(2) A report of the final results obtained in 119 consecutive cases treated by the hanging plaster case is presented. This brings up to date the results of cases treated by this method in our department since a similar report was made, in 1937, of the first 58 cases treated here in this manner.



FIG 9—Roentgenogram of the same patient as shown in Figure 8 five weeks after application of the hanging case.

(3) For consistency in describing end-results, we have again, as in the first report, used the terms "excellent," "good," "fair," and "poor."

(4) Little change has been made in the essential details of this method of treatment since it was first begun. Indications for and exceptions of its use have remained the same.

(5) In several cases of this series, displaced fractures became reduced shortly after application of the encasement. Others were reduced before this was applied.

(6) In fractures of the neck, medial angulation is satisfactorily reduced in some patients by means of a sponge rubber roll placed high in the axilla.

(7) Lateral angulation in fractures of the shaft is corrected by a wedge on the inner side of the encasement at the elbow.

(8) Anterior and posterior angulation is corrected by shortening or lengthening the sling.

(9) Seventy-two fractures of the upper third of the humeral shaft and neck were all successfully treated by the hanging plaster case.

(10) Forty-seven fractures of the middle and lower thirds of the humeral shaft have been treated with satisfactory results.

(11) Early motion of the wrist and shoulder is encouraged. This prevents muscular atrophy and allows early return of maximum function.

(12) The hanging plaster case allows the patient to become ambulatory in a minimum length of time, without having the annoyance of cumbersome appliances necessary for treatment in the abducted position.

(13) The average length of time of treatment in the encasement, for all patients in this series, was approximately six weeks.

(14) The hanging plaster case is economical in that it reduces hospitalization time, dependent care, and the cost of materials used.

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THE EARLY DIAGNOSIS OF POTT'S DISEASE*

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SUCCESSFUL and satisfactory treatment of tuberculous lesions is dependent to a very considerable extent upon early diagnosis. This is as true for Pott's disease as it is for other lesions of tuberculosis. Yet it is common experience that most cases of Pott's disease pass through a long period in which the true nature of the disease is not recognized and diagnoses such as arthritis, myalgia, and sprain are made to explain the patient's symptoms. The true nature of the disease usually is not recognized until the vertebral bodies have undergone such destruction as to cause obvious deformity or until a frank abscess has manifested itself. By that time, the features of the disease in its advanced stages are so obvious that it can be recognized at a glance. Usually, it has taken three or more years to reach this stage. Yet, even in its early stages, Pott's disease presents diagnostic features by which it can be recognized. They are much less obvious than are the features of the later stages of the disease, and in some respects quite different. For that reason, it is worth while to draw attention to them.

Important information from which the early diagnosis of Pott's disease may be made is obtained from three sources: (1) The quality of the pain, (2) the roentgenogram and (3) the recovery of tubercle bacilli from the lesion.

Pain—This is the earliest symptom of Pott's disease, but for a variety of reasons it may not attract attention to the spinal focus. In the first place, the degree of pain often is surprisingly slight. Also, the onset may be so insidious and the progress so gradual that the patient is hardly able to tell when discomfort becomes pain. It is a common experience to have patients with Pott's disease admitted for treatment who have worked, sometimes at such strenuous occupations as farming up to the moment of admission. The slight intensity of the pain and the fact that the patient is still working should not lead us to exclude Pott's disease. On the contrary, a pain which is persistent over a long period of time even though it is of mild degree, demands investigation.

A feature of the pain associated with early Pott's disease, which can divert attention from the real source of the disease is its reference to parts distant from the diseased segment of the spine. The pain of Pott's disease may manifest itself (1) in the back at the level of the disease (*i.e.*, local pain), or (2) in distant areas which are in spinal segments corresponding to the diseased areas (*referred pain*). Local pain and referred pain may both be present at the same time or one or the other may be present alone. The referred pain may be present on one side only or may occur on both sides.

* Presented by title before the American Surgical Association, White Sulphur Springs, W. Va., April 28-30, 1941.

When Pott's disease manifests itself solely or chiefly by referred pain, it is not surprising that attention is diverted from the real source of the disease. Operations for appendicitis and even renal stone are not infrequent in the history of Pott's disease. Subsequent developments demonstrate that these were undertaken for pain referred from spinal disease.

The pain of Pott's disease, nevertheless, presents certain manifestations which should make it easy to recognize as being of spinal origin even though the referred element of the pain dominates the picture. In the first place, bilateral reference of the pain should always make one suspect its spinal origin. Pain on both sides of the trunk or in both legs can only mean (1) bilateral disease, or (2) bilateral reference of pain from a central origin in the spinal column or spinal cord. But the chief distinguishing features of the pain of Pott's disease arise from the fact that it is due to disease of the skeleton and hence is affected by activities in which the skeleton is involved. In any early case of Pott's disease, an inquiry into the factors which intensify the pain will quickly reveal that movements of the spine, increased weight-bearing by the spine (lifting, standing) and jolting of the spine (stepping down steps, riding in a car) all intensify the pain. Sometimes the activities which intensify the pain are so dramatic that they constitute manifestations of particular value. Thus, the explosive muscular efforts of coughing and sneezing cause great intensification of the pain, often spontaneously related by the patient.

Conversely, the pain of spinal disease is relieved by rest. The relief of weight-bearing which occurs when the patient is recumbent, especially if he lies prone and still, is as definite as is the intensification of the pain by movement, increased weight-bearing and jolting.

These aspects of the pain of Pott's disease enable us to recognize its spinal origin. They are not, however, specific for Pott's disease. Any spinal disease manifests itself by this type of pain. But one can, by these features, exclude disease in the area to which the pain is referred and localize the disease in the spine. Other manifestations enable us to recognize the disease as due to the tubercle bacillus.

Roentgenologic Examination—The early radiographic changes in Pott's disease are quite distinctive and characteristic, though they differ greatly from those noted in the later stages of the disease. Little has been said or written regarding these early roentgenographic changes, and because of this the diagnosis of the disease often is postponed until the more familiar radiographic changes of the advanced stages have developed.

The earliest roentgenographic change in Pott's disease is thinning of an intervertebral disk, with or without evidences of destruction of the surfaces of the two adjacent bodies which bound the involved disk. On the evidence of the roentgenogram one is justified in believing that the primary lesion of Pott's disease starts on the inferior or superior surface of a vertebral body, rapidly destroys the intervertebral disk and spreads across it to the adjacent surface of the vertebral body next above it or below. Then follows more or less extensive destruction of the two involved bodies with spread up and down

to other bodies. The very earliest change which is detectable is thinning of the intervertebral disk, and commonly at this stage the carious changes in the vertebral bodies are so slight as to be impossible of detection roentgenologically. It is a characteristic of Pott's disease, however, that the changes in the spine revealed roentgenologically are progressive, so that a series of roent-

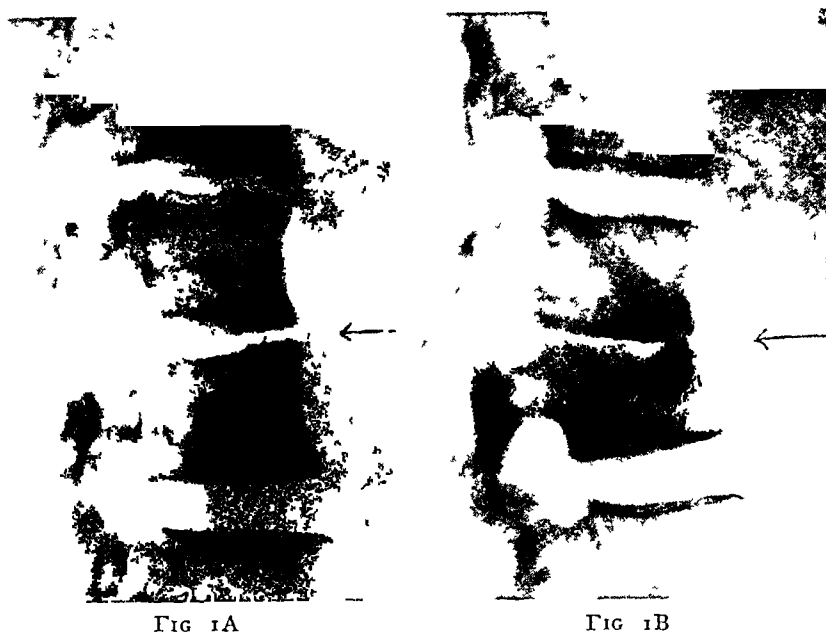


FIG. 1.—Illustrates the value of a thin intervertebral disk as early evidence of Pott's disease.

Female, age 31, in June 1938, commenced to experience pain in back radiating to leg. In July a lumbar abscess formed. It contained tubercle bacilli. Figure 1A is the lateral radiograph, taken in September, 1938. It shows only a thin disk between L V 2 and 3. Figure 1B, taken in September, 1939 shows progress of the disease in one year—destruction of the intervertebral disk, and caries of the body of the 3rd lumbar vertebra. In September 1938, the diagnosis of Pott's disease was confirmed by aspiration, and the recovery of tubercle bacilli in the pus obtained.

genograms, taken at intervals of a few months, reveal first a thin disk, then a thinner disk, with caries of the adjacent surfaces of the adjacent vertebral bodies, finally complete disappearance of the intervertebral disk, advanced caries, and collapse of the vertebral bodies. In the early stages of Pott's disease, the combination of pain, spinal in type, with the appearance of a thin disk in the roentgenogram, is of great significance.

The recovery of tubercle bacilli from a focus of Pott's disease or from the abscess associated with it, is indisputable evidence of the nature of the disease. In the later stages of the disease, this is easy, since an abscess of some sort is commonly present at that stage. It is not so generally known that important information can be obtained by deliberate aspiration of the spinal focus nor is the test commonly practiced. Under roentgenographic guidance it is possible, and not unduly difficult, to pass a long needle into the area of disease. The aspiration of even a small quantity of pus permits accurate diagnosis of the nature of the infection. Occasionally, organisms other than the tubercle bacillus produce spinal lesions indistinguishable by symptoms and

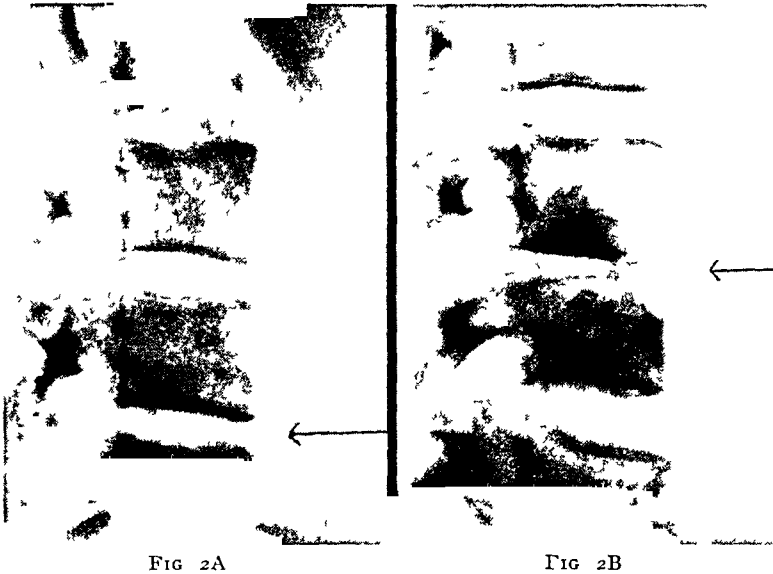


FIG 2A

FIG 2B

FIG 2—Illustrates the value of a thin intervertebral disk as early evidence of Pott's disease

Female age 19 while under treatment for tuberculosis of lung and ankle complained of low back pain radiating to right hip. Figure 2A taken then September, 1938 showed only a thin disk between L V 3 and 4. Figure 2B taken in July 1940 shows the progress of the disease which now presents the characteristic roentgenographic appearance of Pott's disease

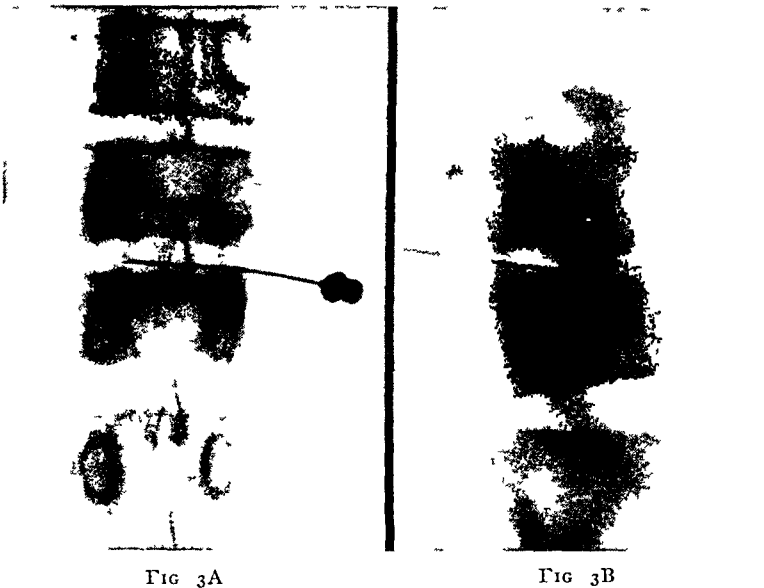


FIG 3A

FIG 3B

FIG 3—Illustrates the value of aspiration in the early and accurate diagnosis of Pott's disease and of lesions resembling Pott's disease

Male age 19. In July 1939 commenced to experience stiffness and aching in back with pain which was accentuated by activity and relieved by rest. Figure 3A and B in September 1939 shows a thin disk between L V 12 and L V 1 and minimal caries of the anterosuperior corner of the body of L V 1. Radiologically the picture is indistinguishable from early Pott's disease. The tuberculin skin test however was negative. Aspiration of the lesion as illustrated yielded a small amount of pus which grew staphylococci. Diagnosis: Staphylococcal osteomyelitis of spine. The course of the disease was satisfactory—early subsidence of the infection, with bony fusion of the involved vertebral bodies

roentgenographic findings from Pott's disease. Aspiration of such foci gives early and accurate information of the nature of the infection.

CONCLUSIONS

The diagnosis of Pott's disease in its earliest stages is a more difficult problem than is the recognition of the disease when well-established. It is important to make the diagnosis as early as possible in order that early treatment may enhance the prospect of cure. Certain of the early manifestations of the disease should be emphasized since their recognition permits early diagnosis.

Pott's disease may be diagnosed in its early stages by three important symptoms and signs:

- (1) Analysis of the pain from which the patient suffers demonstrates that it is of spinal origin (intensification by movement, weight-bearing and jolting, relief by rest).
- (2) The early roentgenographic evidence of a thin intervertebral disk before the characteristic changes of the vertebral bodies is manifest.
- (3) Aspiration of the focus under roentgenographic guidance yields pus from which a positive diagnosis can be made.

"UNEXPLAINED" INFECTIONS IN CLEAN OPERATIVE WOUNDS*

THE IMPORTANCE OF THE AIR AS A MEDIUM FOR THE TRANSMISSION OF PATHOGENIC BACTERIA, AND BACTERICIDAL RADIATION AS A METHOD OF CONTROL

ANALYSIS OF OVER FIVE THOUSAND OPERATIONS, COVERING A PERIOD OF TEN AND ONE-HALF YEARS

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AFTER ten and one-half years of intensive work in an attempt to avoid the operating room infections hitherto frequently referred to as "unexplained," it seems desirable to evaluate the results that have been obtained. Our experience can be divided roughly into three periods (Chart 1)

- (1) Before the institution of bactericidal radiation in the operating room on January 15, 1936—a period of five and one-half years—during which time infections continued to occur despite an increasing knowledge as to their cause and many efforts to eliminate them
- (2) The transition years of 1936 and 1937, during which an increasing number of the staff adopted radiation as part of their "aseptic technic" for an ever-increasing number of their clean operations
- (3) The years 1938-1941,† during which most of the large, clean operations have been performed in a field of sterile air, and infection in any clean primary incision has been extremely rare

For the individual doctor on service, however, the simpler division is into operations performed *without* and the operations performed *with* bactericidal radiation. Regardless of what other measures, in addition to the usually accepted "aseptic and atraumatic technic," have been employed, before or since the introduction of radiation, in an effort to control these infections, the deciding factor in the improvements obtained seems to have been air sterilization.

The results obtained in various types of *large, clean operations* with and without the use of radiation, are summarized in Chart 2. Here it is seen that of a total of 1,735 such operations performed without radiation 207, or 11.9 per cent showed infected wounds. Of these, 19 died as a result of their

* Presented by title before the American Surgical Association, White Sulphur Springs, W. Va., April 28-30, 1941.

† The study was continued to January 15, 1941, in order to give five years' experience with bactericidal radiation but the operations for the 14 days in January, 1941 are included in the 1940 column on each chart.

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infection On the other hand, of 2,463 similar operations performed under bactericidal radiation, wound infection developed in only six, or 0.24 per cent. None of the latter group of infections resulted in a fatality.

In the groups of operations reported (Charts 2-10 and Table I), both with and without radiation, all cases not potentially infected are included.

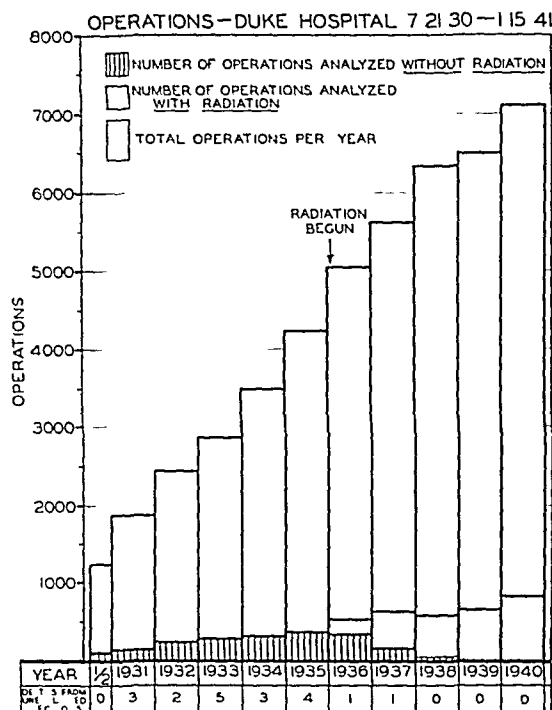


CHART 1—This chart shows in addition to the growth of the Surgical Service of the Duke Hospital for the first ten and one half years:

- (1) The small number of the total operations falling within the groups of large clean procedures (4,585* out of a total of 46,369 [Charts 2-10 and Table I]) which have given us trouble from unexplained infections.
- (2) The distribution by years of all large clean operations which were analyzed in this study (see also Charts 4-10).
- (3) The ratio of the operations used for this analysis (i.e., the larger clean procedures) to the total operations performed approximately 10 per cent, which represents the minimum number in the Duke Hospital which we feel should be performed in a field of sterile air.
- (4) The transition period—1936 and 1937—during which an increasing percentage of the larger clean operative procedures were performed in a field of radiation (see Charts 4-10).
- (5) The period from 1938 to 1941 during which practically all the large operations of the types indicated (Charts 2 through 10) were performed in a field of sterile air.
- (6) The distribution by years of the 19 deaths from "unexplained" infections all of which occurred in the relatively small group of operations (1,782) performed without radiation that were analyzed (see also Chart 3). In the comparable but considerably larger group of clean operations performed (2,600+)—including 140 reopened thoracoplasty wounds—with radiation, there was no death from an infected wound. Any deaths from an infected wound in the remainder of the operations (41,784) had a potential source of infection from the nature of the disease or operation.

* In addition to these operations all of which are tabulated on Charts 2 and 4 through 10 the records of all deaths following operation and not included in these groups (approximately 600) were reviewed to determine the number of patients who died of an unexplained infection in a clean wound (Chart 3).

† Just as in the large clean operations these other operations whether small and clean, grossly contaminated or potentially infected should have bacterial contamination kept to the minimum and the tissues should be left in the best possible condition for healing. However, this subject will not be considered here since it is not the problem with which we are dealing in this presentation.

The charts give a more detailed analysis of the different types of operations by years, the deaths that have occurred as a result of infections in clean wounds, the organisms that have caused the infections, and the improvement that has been obtained, predominantly by an sterilization.

Occasionally, the criticism has been made that the good results which we claim to have been obtained by air sterilization (Charts 2-10 and Table I) have been brought about by other improvements in technic. Many others who do not make this criticism at least raise this question. The answer is that for five years, and particularly after the disastrous three months in

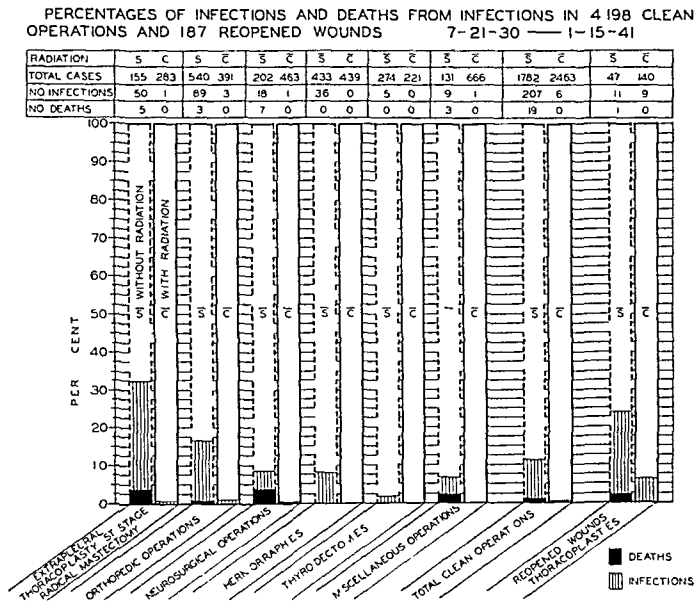


CHART 2—This chart shows in summary for comparison the results obtained without and with radiation in several types of clean primary operative procedures and in a group of reopened thoraco-plasty wounds. The latter group of cases are recorded separately since they present a risk of infection as described under second and subsequent stage thoracoplasty (Chart 5) which is not present in clean primary incision. At the top are given the actual number of cases, the number of infections and the number of deaths from infections for each group while immediately below in the chart these figures have been transposed into percentages, for more accurate comparison of the results obtained without and with radiation in each type of operation. Deaths from 'unexplained' infections have been eliminated when bactericidal radiation was used.

1933-1934 (Chart 3), we tried every improvement in technic that seemed feasible and to offer any hope of success, but without notable results, until the air-borne pathogenic bacteria (probably given off from the respiratory passages of the occupants of the operating rooms) were largely eliminated by ultraviolet radiation. Since this source of contamination (which we consider to overshadow all others where good technic, as we know it to-day, is used) has been largely eliminated, most of these previously adopted additions to technic, conceived in desperation and of questionable value have been discarded.

For the information of those who feel that the improvement in our results was brought about by changes in technic other than air sterilization, these changes and additional precautions taken by us before beginning air sterilization in an effort to control these infections were given in a chronologic order but had to be eliminated from this publication because of its length. It will be seen, however, from an analysis of the charts, that the virtual elimination of operating room infections on different surgical divisions varied

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INFECTIONS IN CLEAN WOUNDS CAUSING DEATH (7-21-30 TO 1-15-41)

1931	MARCH 21 MARCH 27	EXPLORATORY LAPAROTOMY CRANIOTOMY	PERITONITIS MENINGITIS	HEMOLYTIC STREPTOCOCCUS STAPHYLOCOCCUS ALBUS
	DECEMBER 22	CEREBELLAR	MENINGITIS	STAPHYLOCOCCUS ALBUS
1932	FEBRUARY 2	ARTHRORASTY HIP	SEPTICEMIA	BETA HEMOLYTIC STREPTOCOCCUS B. COLI COMMUNIOR
	NOVEMBER 1	SECTION 5TH NERVE	MENINGITIS	SMEAR-GRAM POSITIVE COCCI IN CLUMPS
	JANUARY 12	SPLENECTOMY	PERITONITIS	STAPHYLOCOCCUS AUREUS
1933	NOVEMBER 15 DECEMBER 6 DECEMBER 22 DECEMBER 28	THORACOPLASTY 1ST STAGE THORACOPLASTY 1ST STAGE OSTEOTOMY FEMUR THORACOPLASTY 2ND STAGE	PULMONARY EMBOLI SEPTICEMIA EXTENSIVE INVASION NO BLOOD CULTURE	HEMOLYTIC STAPHYLOCOCCUS AUREUS HEMOLYTIC STAPHYLOCOCCUS AUREUS BETA HEMOLYTIC STREPTOCOCCUS, STAPH AUREUS STAPHYLOCOCCUS AUREUS
	JANUARY 16 JANUARY 26	RADICAL MASTECTOMY SECTION 5TH NERVE	SEPTICEMIA MENINGITIS	HEMOLYTIC STAPHYLOCOCCUS AUREUS HEMOLYTIC STAPHYLOCOCCUS AUREUS
1934	OCTOBER 31	SECTION 5TH NERVE	MENINGITIS	HEMOLYTIC STAPHYLOCOCCUS AUREUS
	APRIL 17	THORACOPLASTY 1ST STAGE	(CHILL -- NO BLOOD CULTURE	HEMOLYTIC STAPHYLOCOCCUS AUREUS
1935	SEPTEMBER 16 OCTOBER 12 OCTOBER 22	CEREBELLAR THORACOPLASTY 1ST STAGE FUSION KNEE JOINT	MENINGITIS SEPTICEMIA SEPTICEMIA	GRAM POSITIVE DIPLOCOCCUS HEMOLYTIC STAPHYLOCOCCUS AUREUS BETA HEMOLYTIC STREPTOCOCCUS STAPH AUREUS
	APRIL 20	CRANIOTOMY **	MENINGITIS	STAPHYLOCOCCUS AUREUS -- HEM & NON-HEM
1936				
1937				
	DECEMBER 9	EXCISION TUMOR NECK **	NO BLOOD CULTURE	HEMOLYTIC STAPHYLOCOCCUS AUREUS
1938 1939 1940				

* FIRST RADIATION UNIT IN OPERATING ROOM INSTALLED 1-15-36

** RADIATION NOT USED

CHART 3—The fatalities from infection in clean wounds occurred only following operations where radiation was not used and were largely confined to neurosurgical, thoracic and orthopedic operations. The four exceptions were two debilitated patients having celiotomies (inoperable carcinoma of the stomach and cirrhosis of the liver with ascites), one woman of 73 having a radical mastectomy and one man of 67 having an excision of a malignant tumor of the neck by a surgeon who was not accustomed to such a procedure.

The 19 fatal infections all occurred during the cooler months of the year during which time in general the air contamination is highest. Eleven, or 58 per cent, became infected during November, December, January and February, five or 26.3 per cent, during October and March, and three or 15.7 per cent during September and April. There was no death from such an infection during May, June, July and August. In this chart each monthly division is blacked out if one or more deaths occurred during the month. Note the proximity of the "black months" to the heavy lines dividing the chart into years.

Particular attention is also called to the disastrous three months of November, December, and January, 1933-1934, during which time there were six deaths from "unexplained" infections in clean wounds. Thus over a period of ten and one half years 31.6 per cent of all the deaths from "unexplained" infections occurred during a three month period in a consecutive group of only 1.5 per cent of the total number of patients operated upon. A similar "epidemic" of operating room infections seemed to be under way in September and October 1935, but was halted by discontinuing performing large operations that were not emergencies. At this time all patients in the hospital for extrapleural thoracoplasty were sent back to the sanatorium to await the months of lower air contamination or the completion of the preliminary experiments with, and the installation of adequate radiation equipment in the operating rooms.

There have been only two deaths from "unexplained" infections since the first radiation unit was installed and in neither of these was it used. The left craniotomy April 20, 1936 for what was considered before and found at operation to be an inoperable glioma, was performed without radiation since the only room equipped for radiation was in use for a laminectomy for removal of a benign spinal cord tumor.

The excision of the tumor of the neck December 9 1937 was performed by a surgeon who had never used bactericidal radiation and who was inexperienced in neck surgery. The subsequent infection, caused by the hemolytic *Staphylococcus aureus* spread extensively along the fascial planes, causing the patient's death. No blood culture was taken.

† This percentage is all the more impressive when consideration is given to the fact that after the epidemic of infections in November, December and January, 1933-1934, large clean operations of election were postponed until the months of low air contamination and for operations that could not be postponed until the summer an attempt was made to anticipate and avoid the periods of greatest danger by daily cultures of the air in the operating rooms (References 3 and 12).

as to time, but in each it was simultaneous with the adoption of air sterilization. The improvement in results beginning with the institution of radiation has persisted despite the abandonment of many of the previously adopted precautions.

Undoubtedly, since 1936, there has been some improvement in wound healing as a result of our return to the use of silk in certain wounds, and as a result of the discontinuance of drainage in others. This is not the explanation of the virtual elimination of wound infections, however, as is illustrated by the fact that we were "brought-up" on silk technic, abandoned it temporarily only because of the prevalence of "unexplained" infections, and began using it again only after these "unexplained" infections had been explained and virtually eliminated by the use of ultraviolet radiation. Drainage of thoracoplasty wounds was begun as a result of frequent infections and was discontinued following the institution of radiation, but only after great improvement in wound healing had been obtained and after the drains in a number of cases had been cultured and no growth had been obtained. Catgut as a suture material is still used for all thoracoplasties, and there has been no change in the suture material used for neurologic and thyroid surgery (silk), and orthopedic surgery (catgut). During the past two years we have discontinued drainage of radical mastectomy wounds when radiation is used and find that, as a rule, they do not fill up with lymph, serum, or blood.

Previous publications on radiation have detailed

- (1) The bactericidal and fungicidal effect of this radiation²
- (2) The effect of radiation on wound healing^{3, 4}
- (3) The reduction in the number of wound infections in small series of operations^{5, 6, 7}
- (4) The reduction in the postoperative temperature reaction⁸
- (5) The rôle of the respiratory tract in contamination of the air¹³

The present report covering a period of ten and one-half years, can be divided roughly into two parts. (I) An analysis of all deaths from infection following a clean operation* during the time covered, and (II) an analysis of 1,313 selected clean operations (but including 47 reopened thoracoplasty wounds) before radiation was instituted, January 15, 1936, 469 similar clean operations performed without radiation after January 15, 1936, and all operations—2,803—(including 140 reopened thoracoplasty wounds [Chart 5] and something less than 200 potentially infected operative wounds, the latter included in the 866 miscellaneous operations [Chart 10]) performed with bactericidal radiation from January 15, 1936 to January 15, 1941.

(I) DEATHS

From July 21, 1930 to January 15, 1936 (when bactericidal radiation was first instituted), 15,674 operations of all types (Chart 1) were performed

* Exclusive of Obstetrics and Gynecology, which is a separate service.

with 16 deaths from infections in clean primary incisions, and one death from infection in a clean reopened thoracoplasty wound. In contrast to this, during the five-year period, from January 15, 1936 to January 15, 1941, with a total of 30,695 operations (Chart 1) there have been *only two deaths* from infections in clean incisions, either primary or reopened, and both of these infections occurred in wounds that were not protected during operation by bactericidal radiation (Chart 3).

Particular attention is called to the fact, as shown in Chart 3, that each of the 19 patients who died from an infection in a clean incision had had a large operative procedure of a specialized type, with the exception of two debilitated patients who had a celiotomy which was followed by peritonitis.

Since deaths from infections in "clean wounds," where radiation is not used, are relatively rare and occur almost entirely in a few types of the larger procedures or in debilitated patients (Chart 3) they will be seen only rarely by the average surgeon. For them the elimination of the somewhat more frequent nonfatal infections and the improved healing in all wounds, even where the contamination does not go on to gross suppuration,* probably results in a greater sum total of good than the saving of an occasional patient from the very rare fatal infection.

(II) INFECTIONS

All operations of several types† (Charts 1-10 and Table I) performed during a period of ten and one-half years have been reviewed. The post-operative notes and the temperature chart of every record have been reviewed in order to pick up any infections that may not have been included in the index file of postoperative infections. This was particularly important for the orthopedic operations, where the wound was under an encasement which frequently was not removed and the infection not diagnosed until a return visit to the Out-Patient Dispensary,‡ at which time the hospital record had been completed and indexed.

* The improvement in wound healing and the diminished systemic temperature reaction, both elevation and duration, brought about by radiation has been reported for small groups of cases (extrapleural thoracoplasties, radical mastectomies, and herniorrhaphies). These results, as given in a previous report,⁸ were so conclusive, and such an analysis is so laborious and time-consuming that it did not seem to be necessary or desirable to carry it out here with such a large series. The surgical staff, from clinical observation, are of the opinion that this average of diminished systemic temperature reaction as reported has been maintained throughout the entire series of operations where bactericidal radiation has been used.

† With the exception of an occasional record that could not be located.

‡ Some of these patients had their follow-up treatment in various Orthopedic Clinics over the state, so that our follow-up records were not complete. As a result, some mild or moderate infections, particularly where radiation was not used, undoubtedly have been missed.

Stitch abscesses were omitted* for the entire group both with and without radiation since they are considered to be the reaction to a foreign body. They are particularly likely to develop when the suture is left in for too long a time, with the growth of the skin organisms already present. In no respect can they be considered as operating room infections, except on the very unlikely possibility that the sutures themselves were unsterile.

Unexplained operating room infections, particularly those of a serious nature, occur in only a small percentage of the general run of operations performed by well trained surgeons with a relatively good "atraumatic technic." However, during and following certain of the larger procedures, such as many of those included in this analysis, large areas of tissue are exposed for a long time, excessive trauma may be unavoidable, hemostasis may be difficult to obtain, dead space may not be obliterated, the patient may be in a debilitated condition or the tissues may offer little resistance to infection, cleavage planes or spaces may be opened for the relatively unimpeded spread of infection, immobility in the wound may be unobtainable, or packs or drains may have to be inserted, thus making it more likely that the organisms gaining access to the wound can cause an infection.

Furthermore, it is well known that at certain times the danger of "unexplained" infection in clean operative wounds is far greater than the average (Chart 3). Such a peak of danger with us is well illustrated in Chart 3, where it is seen that for the past ten and one-half years, since the opening of the Duke Hospital, 31.6 per cent of all the deaths (six patients) from "unexplained" operating room infections in clean wounds occurred during the three consecutive months of November, December, and January of the academic year 1933-1934. The total number of operations performed during these

* In previous publications, the cases which we did not consider to have an operating room infection but which had a positive culture report on the record, were included with the abstracted infected cases, and the decision as to the true nature, origin, and severity of the condition was left to the reader. Such a policy could not be followed in this larger analysis since the results are presented in the form of charts. In order that the reader may make his own decision in these cases, reference is given to those previously published abstracts of operations which are omitted from the charts in this report since we do not consider them to have had "unexplained" operating room infections.

Abstracts in Reference 7

Cases—(1) Inguinal hernia—stitch abscess, (2) cerebellar exploration—stitch abscess, (3) laminectomy, fractured spine—contused wound with skin abrasions preoperative, but infection considered to be hematogenous, (4) arthroplasty hip—postoperative hemorrhage, drains left in wound, and (5) open reduction fracture-dislocation ankle—skin slough with superficial infection limited to area of slough.

Abstracts in Reference 9

Cases—(1) Inguinal herniorrhaphy—skin inversion only, (2) radical mastectomy—stitch abscess, (3) extrapleural thoracoplasty through scar—stitch abscess, maceration suture line, (4) extrapleural thoracoplasty, second stage—stitch abscess, (5) extrapleural thoracoplasty, first stage—pustular eruption (operative site before operation delayed healing of skin incision made with cutting electric current), and (6) extrapleural thoracoplasty, second stage (same patient as [5])—draining hematoma.

three months was only 708, or 15 per cent of the total of 46,369, for the ten and one-half-year period (Chart 1)

In analyzing these statistics on infections (Charts 1-10 and Table I) one should keep in mind that many of the operations reported (both with and without radiation) were the larger procedures, and, therefore, the ones most likely to become infected (Ref Chart 1 for percentage of total operations included in these groups)

The operating room infections both with and without radiation have been classified as mild, moderate, severe, and as having caused the death of the patient

(1) The mild infections were trivial, with little local or systemic reaction, and the minimum amount of pus

(2) Those classed as moderate produced more systemic and local reaction and contained more pus than the mild group

(3) Every infection with extensive involvement of the wound or a severe local or systemic reaction which did not kill the patient, was classed as severe, regardless of whether or not the life of the patient was threatened

(4) Those classified as deaths from infection are self-evident. They are also listed separately in Chart 3, and have occurred only when bactericidal radiation was not used and following an extensive operation or an operation upon a debilitated patient

The operations of each type covered by this survey can be divided roughly into three groups

(1) All those performed during the first five and one-half years before bactericidal radiation was instituted. In this series the infection rate was highest, and the infections of greatest severity despite the many things that were tried in an effort to prevent them

(2) All operations of the types analyzed, and performed without bactericidal radiation during the transition period from January 15, 1936 through 1938. In general, during this period (Charts 4-10 and Table I) the percentage of infections in operations where radiation was not used was lower, and when they occurred they were much less severe than in the previous years. This is explained by the fact that any service or any individual at first performed only the larger operative procedures, and, therefore, the ones most likely to become infected, in a field of bactericidal radiation, thus eliminating them from the nonradiated group. As the good results obtained in these larger operations became evident, an increasing percentage of the operations of less magnitude was also performed in a field of sterile air

Operations performed without radiation after 1938 are not included in the charts since they were so few in number, usually small in size and frequently performed during the summer months when the air contamination was low, so an analysis would give no true idea of the risk of infection in the general run of such operations

(3) In this group are all operations performed in a field of bactericidal

radiation after beginning its use for operations upon patients, January 15, 1936 (in general, the operations of greatest magnitude for any service or any individual during the period of transition, 1936-1938). Originally, sterilization of the air in the operating room by ultraviolet radiation was used only during extrapleural thoracoplasties, and no such operation has been performed without it since the first radiation unit was installed (Charts 4 and 5). Radical mastectomies were soon brought into the radiation group. The orthopedists gradually began using it for their larger operations in 1937 (Chart 6). The neurosurgeons began using it during 1936 (Chart 7) but temporarily abandoned it in the fall and winter of 1937-1938, for reasons explained in the text for Chart 7. Early in 1938, after the occurrence of a number of infections, it was resumed by this service for all except small procedures such as trephines, and infected cases which had to be drained (Chart 7).

Thyroids and herniae, because of their lesser magnitude, and because of the shortage of suitably equipped operating rooms, were only gradually brought into the radiation group (Charts 8 and 9). Radiation was used first in these operations, predominantly, for the larger operations and during the winter months when the air contamination was high, but later, in an increasingly high percentage of cases, throughout the entire years*.

Since early in 1936, an increasing number of miscellaneous operations, a fair percentage of which were potentially infected, have been operated upon with radiation. These are all grouped together in Chart 10.

Charts 4-10, inclusive, show the incidence of infection in these various operative groups by years, with and without bactericidal radiation. In each group, a striking reduction in the frequency of wound infection occurred when radiation was used. In first stage thoracoplasties and radical mastectomies the infection rate dropped from 32 to 0.35 per cent, in orthopedic operations from 16.5 to 0.74 per cent, in neurosurgical operations from 9 to 0.22 per cent, in hemorrhaphies from 8.3 to zero per cent, and in thyroidectomies from 1.8 to zero per cent.

The criticism can be made justly that the experiment would have been more accurately controlled had alternate operations in each group been performed with and without radiation. However, by the time the radiation technic had been worked out, 17 patients had died as a result of an infection which we now consider to be largely preventable (Chart 3). Many others had had a needlessly prolonged convalescence and impairment of their operative results, while still others, because of the danger of infection at times of high air contamination, had been refused the advantages offered by operation. It did not seem to us justifiable, for the sake of the experiment, to subject any of these patients to a risk, which we were reluctant to take before bactericidal radiation was available.

* Radiation was started by one of us as an experimental project, to determine the effect of the elimination of air-borne bacteria during the operation on wound healing. Since that time all members of the surgical staff (General, Neurologic, Orthopedic, Plastic, Thoracic and Urologic) have, at their own request, adopted it as routine for their large clean operations.

The effect of this "fear of infection" on the growth of the Thoracic and Neurosurgical Services during 1933, 1934, and 1935, is illustrated in Charts 4, 5 and 7. In contrast to the continued growth of the entire service (Chart 1) the number of these operations per year remained at a standstill or actually diminished from 1933 through 1935, because of the hesitancy of the staff, except in emergency, to advise these large operations during certain times of the year when the air contamination was high.

A notable example of the effect of these infections and deaths on our method of treatment of patients, is the fact that after the fatalities from meningitis following section of the fifth nerve (Chart 3) most of these patients were treated by alcohol injection. Only after radiation had been instituted and proved to be an effective means of protecting these open wounds, did we resume section of the nerve by open operation. Beginning in 1936, the full year was made available for these more extensive operations by air sterilization, and immediately there was a great increase in the number of such operations performed (Chart 7).

THORACOPLASTY, FIRST STAGE, AND RADICAL MASTECTOMY—CHART 4

These two types of operation are combined to conserve space. Both involve wide exposure of tissues and, in our hands, had a high infection rate (25–38 per cent^{7, 6, 9}), but with the more serious infections and the greater number of fatalities from infection in the thoracoplasty group (Chart 3). Otherwise, they are radically different in that the thoracoplasties are associated with more trauma, hemostasis is less satisfactory, there is residual dead space which cannot be obliterated, and there is more motion in the wound during the convalescent period. Before radiation was instituted, catgut was used for both, but since 1936 most of the mastectomies have been performed with silk while catgut is still used for the thoracoplasties. The unfavorable conditions for healing of the mastectomy wounds are the poor blood supply to the skin flaps, the tension which is at times present, and the occasional accumulation of lymph or blood beneath the flaps.

The diminishing number of operations each year, for 1933, 1934, and 1935, was a direct result of our refusal to operate upon patients for thoracoplasties during the winter months and the limited bed facilities during the summer. The two fatalities from infection in thoracoplasty wounds during 1935 occurred in April and October (Chart 3), at the beginning and end of what, at that time, we considered to be the best season for operating upon these patients. Because of the large number of patients needing this operation we had started "crowding the season" by admitting these patients in March and continuing to perform these operations in the fall. However, after the fatality in October the other patients in the hospital for thoracoplasty were discharged without operation.

The number of thoracoplasties performed in 1936 and 1937 was limited only by the beds available. The diminution in the number of these operations

per year, during 1938, 1939, and 1940, has been the direct result of the building of operating rooms by the state hospitals for tuberculosis* and the shifting of our work more to intrathoracic tumors, pneumonectomies, and lobectomies, which are not included in this chart but in the group of miscellaneous operations (Chart 10)

THORACOPLASTIES, SECOND AND SUBSEQUENT STAGES†—CHART 5

These operations are placed in a separate chart as potentially infected since a reopened recent operative wound has two sources of infection which do not exist in the primary incision. The first of these is that the few organisms gaining entrance to the wound during the previous operation may find a harbor about a catgut suture, or in a collection of fluid in a dead space, multiply, but not give evidence of suppuration, and be present in much larger numbers to inoculate the second operative wound when fresh tissues are laid open. The second is that the organisms present in the deeper layers of the skin (hair follicles and sebaceous glands) may have grown along the skin sutures of the first closure which act as foreign bodies and form cleavage planes through the tissues. If the sutures are tied tightly, they constrict the blood supply and may cause necrosis, but under any condition diminish the resistance of the tissues to invasion by the organisms which are always present in the skin. Occasionally, if the sutures are left in for a relatively long period, a droplet of pus may be produced around one or more of them and present at the point where the suture pierces the skin—the well known stitch abscess. These have nothing to do with an operating room infection and, as already noted, are omitted from this statistical study both for the radiated and nonradiated operations. Certainly, in the case of stitch abscesses and undoubtedly, about many sutures where there is no gross evidence of pus, there must be a growth of the skin organisms. When the incision is reopened 14–20 days after the preceding operation, and six to 15 days after the sutures have been removed, the scalpel must, in certain cases, pass through clusters of these organisms of relatively low virulence which are still viable. As a result, a low grade infection may result. In our cases, such an infection was usually restricted to the subcutaneous fat or to a collection of fluid in the wound. We feel that this latter explanation accounts for most of the infections in this group of reopened thoracoplasty wounds where radiation was used and for at least a part of the infections in this group where radiation was not used.

It has been observed also that where radiation was not used the infections

* See note under Thoracoplasties, Second and Subsequent Stages for the experience of Doctor Monroe at one of these hospitals.

† Since this chart was originally designated to include all potentially infected thoracoplasties, one first-stage thoracoplasty—grossly contaminated by a considerable quantity of germ-laden perspiration during the operation—is included, and accounts for one of the two operative wounds classed as severely infected when radiation was used in 1936 (Case 3, Reference 9)

INFECTED OPERATIVE WOUNDS

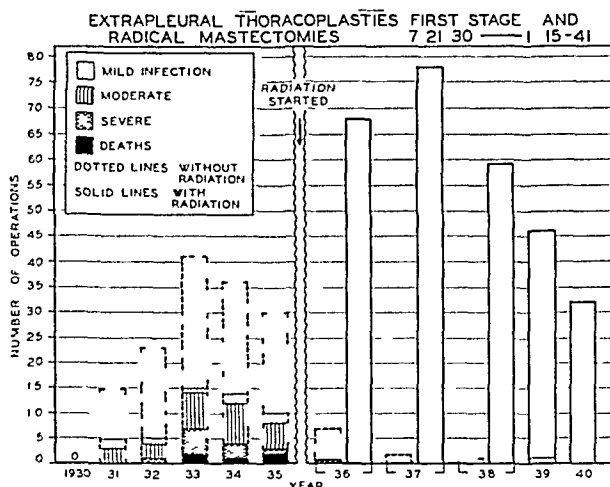


CHART 4—Note the high infection rate before radiation was instituted with only one *questionable mild infection** in a much larger series of similar operations where radiation was used

The lack of growth of this service in 1934 and 1935 was caused by the refusal of the staff to perform these operations during much of the year because of the "fear of infection." The rapid growth in 1936 and 1937 resulted from the removal of this fear by air sterilization and was limited only by the beds available for such cases. The drop in 1938-1940 resulted from the opening of surgical services at the State hospitals from which most of our patients had been referred. For a more careful analysis and for the experience of Doctor Monroe in reducing the infection rate for thoracoplasties at one of the State hospitals from 22.7 per cent to 1.09 per cent by the introduction of ultraviolet radiation for air sterilization see the text under Thoracoplasties, First Stage and Second and Subsequent Stages.

* The "mild infection" in 1939 was thought by the operator to be only an hematoma, and drainage ceased within two days. Cultures, however, revealed both the *Staphylococcus aureus* and *albus*. Excision of an enlarged lymph node during the course of an apicolysis would, at least have to be considered as a possible source of the infection if such existed. The organisms obtained by culture may have been from contamination with skin organisms at the time the culture was taken (for abstract see Case 6, Reference 7).

in reopened thoracoplasty wounds were less numerous, less severe, and less likely to be fatal than the infections occurring in the primary thoracoplasty incisions⁹ (compare Charts 4 and 5). To us, the most logical explanation of this seemed to be that the patient, following the first operation, developed a certain amount of immunity, as is known to occur in the peritoneal cavity following multiple celiotomies for intestinal surgery. Even in these reopened, potentially infected wounds, with the introduction of bactericidal radiation the percentage which became infected was reduced from 23.4 to 6.4.

The effects of the fear of infection in extrapleural thoracoplasties on the growth of the service, during 1933, 1934, and 1935, are illustrated in this chart as in Chart 4. The drop, during and since 1938, followed the opening of operating rooms at the State Hospitals for Tuberculosis.

The experience of Dr. Clement R. Monroe¹⁰ with infections at the State Sanatorium, Sanatorium, N. C., since opening their operating room, was given in a recent personal communication as follows:

"Before installing ultraviolet radiation at the State Sanatorium, we performed 75 thoracoplasty stages, with 17 severe infections. Since this installation we have performed 92 such operations, with the following results from the standpoint of infection:

- Severe infection—1—following *second-stage operation*
- Stitch abscess—3—following *second-stage operation*
- Stitch abscess—1—following *third-stage operation*

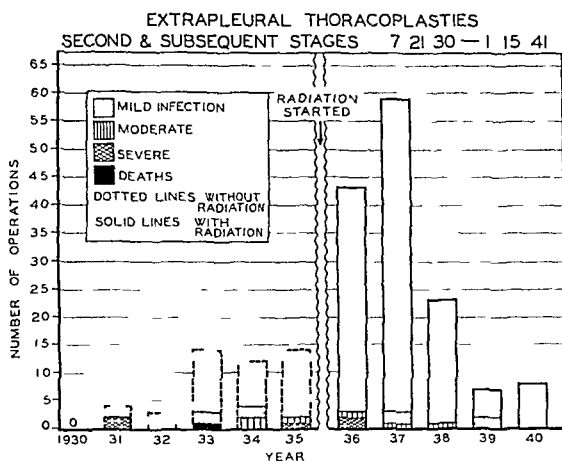


CHART 5—Reopened wounds have a potential source of infection from organisms already present in the wound. These may have gained entrance at the preceding exposure or may have grown down along the skin sutures. Under either condition having increased in number they may contaminate the tissues exposed at the subsequent operation sufficiently to cause gross suppuration. In our opinion the few infections in these reopened wounds where radiation was used may be explained on this basis. For explanation of the few operations in 1934 and 1935, the great increase in 1936 and 1937, and the few since 1938, see the legend to Chart 4. See text for more complete analysis.

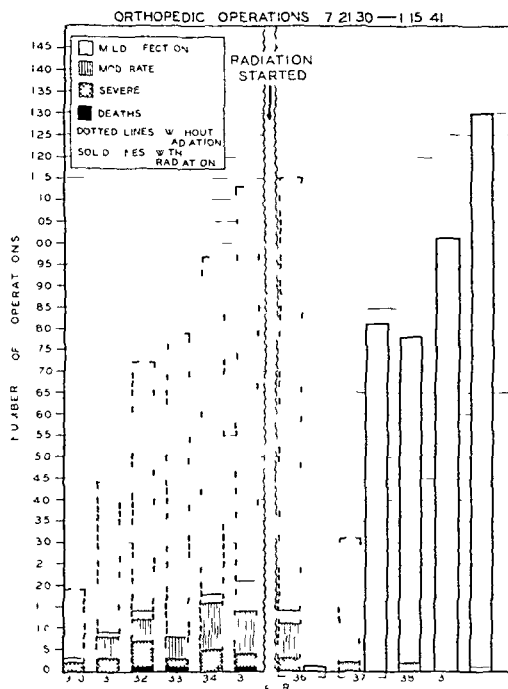


CHART 6—The improvement in the infection rate in orthopedic operative wounds occurred in 1937 simultaneously with the adoption by this service of radiation for their larger operative wounds.* Compare with other charts in all of which the improvement in the infection rate varied as to time but was definitely correlated with the institution of radiation. See text for more complete analysis.

The mild infection (?) in 1940 was recorded six days following bilateral operations for hallux valgus which was described as "pus" was expressed from the wound on the right foot. Cultures failed to reveal any growth of organisms and the wound was described as "healing under compresses without complications."

*The two infections charted as moderate in 1938 were as follows:

- (1) One patient with a comminuted fracture of the patella, syphilis, and delirium tremens walked around on the second and third days after an open reduction and developed an hemarthrosis. The fluid on evacuation contained the *Staphylococcus aureus*. The wound continued to drain and the patient developed an osteomyelitis of the patella.
- (2) Another patient with a triple arthrodesis for flaccid talipes equinovarus developed a large area of skin slough with a mixed infection (*Beta hemolytic streptococcus* and hemolytic *staphylococcus aureus*) in the wound. We cannot state whether or not this would have developed had there been adequate blood supply to the flaps.

" We not only have many less infections but the postoperative courses are much better in all respects. I have now reached the point where I think I would hesitate a long time before undertaking a thoracoplasty in an operating room not equipped with ultraviolet radiation."

ORTHOPEDICS—CHART 6

Since sterilization of the air in the operating room was undertaken as an experimental project by one of us and at first only one operating room was available, it was not used by the orthopedists, except for one case, until 1937, and then only for their larger procedures. The improvement with its use in these cases was so striking that, by 1938 it was used by them for most of their clean operations.

The year 1937 offers a striking illustration of the reduction in the infection rate in the nonirradiated operations brought about by a selection of cases so that the operations more likely to become infected were performed with bactericidal radiation. Whereas formerly the infections in clean orthopedic wounds ranged from 10–20 per cent (average 16.5 per cent) for different years, during this year only 6 per cent of these nonirradiated clean operative wounds became infected and, then the infections were of only moderate severity.

The large number of orthopedic operations in this report results from the high percentage of clean operations on this service, and the inclusion of many operations of smaller magnitude, such as excision of a semilunar cartilage or even an operation for hallux valgus. The percentage of infections in the larger arthroplasties alone was, therefore, higher than the infection rate for the entire group as shown by Chart 6.

The drop in the number of clean operations on this service, beginning in the fall of 1937 and 1938, was due to changes in personnel.

NEUROSURGERY—CHART 7

Chart 7 gives a striking illustration of the fact that in these patients, when an operative wound becomes infected, it is more likely than in any other type of operation to be fatal. This is particularly true for infections with some of the less virulent organisms which in the usual wound would produce only a mild reaction but in neurosurgery may cause a fatal meningitis (Chart 3). All these patients who died of infected wounds following clean operations developed a meningitis, two of them with the *Staphylococcus albus*. Chart 7, along with the others, illustrates, clearly, that the infection rate changed little during 1936 and subsequent years except insofar as it was influenced by bactericidal radiation.

The fear of infection also limited the growth of this service during 1933, 1934, and 1935. As an example, during this period open operations upon patients suffering with trifacial neuralgia were virtually abandoned in favor of alcohol injections. The small percentage of neurosurgical patients operated upon with radiation during 1936 was the result of a shortage of suitably

equipped operating room space, and the difficulty encountered in working out for the operator an adequate protection which still permitted the use of a head

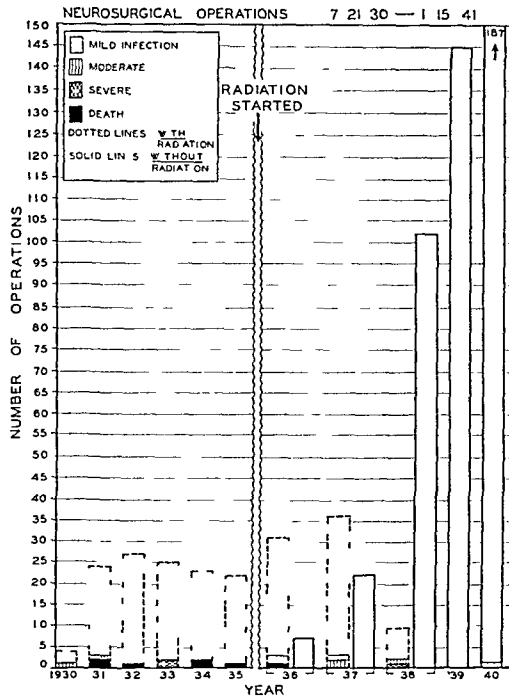


CHART 7—Air sterilization was not adopted for all clean neurosurgical operations until early in 1938 for reasons as explained in the text. Infections have been practically eliminated* where radiation was used. This chart also illustrates the lack of growth of the service during 1933, 1934, and 1935 resulting from the 'fear of infection' as noted in the legends for Charts 4 and 5. See text for more complete analysis.

* The patient recorded as having a mild infection in 1940 developed two stitch abscesses four days following a cerebellar operation. No culture was made. On the seventeenth postoperative day, two small collections of pus were evacuated from the incision at the site of the stitch abscesses and cultures showed the hemolytic *staphylococcus aureus*. The wound had been closed with buried and skin sutures of silk. A spinal fluid fistula later opened at the site of the stitch abscesses. The patient died on the forty-fifth postoperative day as a result of the continuation of the tumor growth with an hemorrhage into the tumor. This infection was not classed as a stitch abscess because of the subsequent evacuation of pus. However, the organisms may have entered about the skin sutures and have been harbored about the buried silk sutures.

(During this same year a child with 'maceration of the skull' for oxycephaly twice pulled off her dressings fingered the wound developed a skin slough from the tension which was so great that the wound could scarcely be closed and subsequently had an infection with the nonhemolytic *staphylococcus aureus*. Both the operator and I considered this infection to be secondary to the skin slough and subsequent contamination so it was omitted from the chart but is mentioned here for completeness.)

lamp. During 1937, an increasing percentage of these operations were performed with radiation until September, when a change in personnel again raised the difficulties of an individual adjusting his operating technic, with the use of a head lamp, to adequate protection of himself. At this time, radiation was abandoned completely until early in 1938, with the resultant infections as shown in the chart for 1937 and 1938. Since early in 1938, radiation has been used for all large clean neurosurgical operations.

HERNIORRHAPHIES—CHART 8

The infections in hernia wounds without radiation were usually mild or moderate but are of serious import since they predispose to a recurrence.

INFECTED OPERATIVE WOUNDS

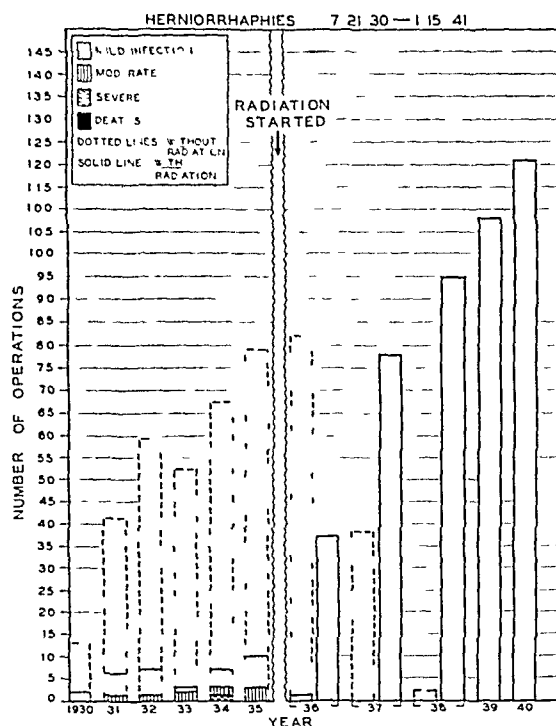


CHART 8—Infections in hernia wounds were never severe or frequent enough to interfere with the growth of the service, but did cause the temporary abandonment of the "silk technic." After the institution of radiation, silk was again used in all clean hernia operations. The absence of infection and the improved healing brought about by a diminution in the wound contamination and the use of less irritating suture material has undoubtedly resulted in a diminution in the percentage of recurrences.*

* The statistics on infections in hernia wounds were obtained from Dr William F Hollister, who is making a survey of the postoperative results. This survey has not been completed, but it seems safe to prophesy that since the institution of bactericidal radiation and the return to silk technic, the percentage of recurrence after comparable periods of time will be greatly reduced.

THYROIDECTOMIES—CHART 9

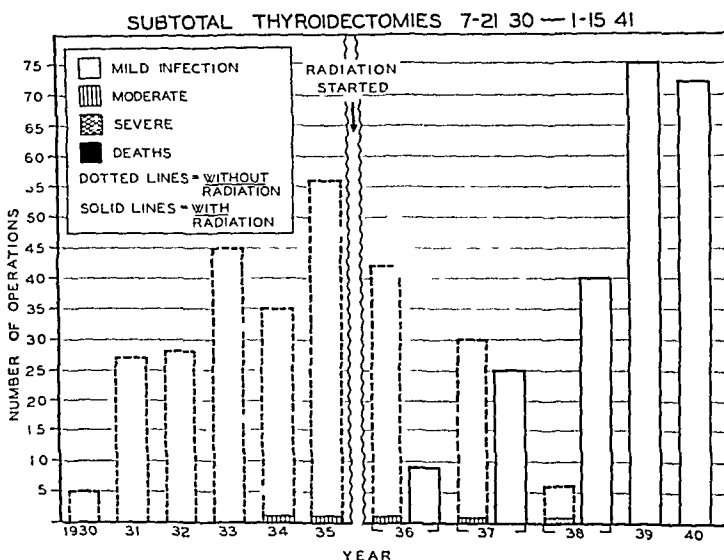


CHART 9—Before beginning the use of radiation, infections in our thyroid wounds were rare and no infection was severe or fatal so there was no curtailment in the growth of this service because of "fear of infection" and silk was never abandoned. Air sterilization, however, has produced an appreciable improvement by the elimination of the occasional moderate infection that had occurred when the air was not sterilized.

This analysis should be interpreted with the following facts in mind

(1) After 1936, silk was again used (it had been abandoned previously because of the recurring infections) for all hernia operations and this, of course, had its effect in securing improved wound healing

(2) The skin in the inguinal region, as contrasted to most other areas of the body, has a much larger number of bacteria present toward the end of an operation, particularly when the patient is perspiring freely

(3) Some of the herniae were large, as the incisional, and umbilical, while others, particularly the inguinal herniae in children, were small

(4) With the institution of bactericidal radiation for the larger hernia operations, during 1936 and 1937, infections were almost eliminated (It should be emphasized again that all feasible precautions were already in use to protect the open wound from the skin organism)

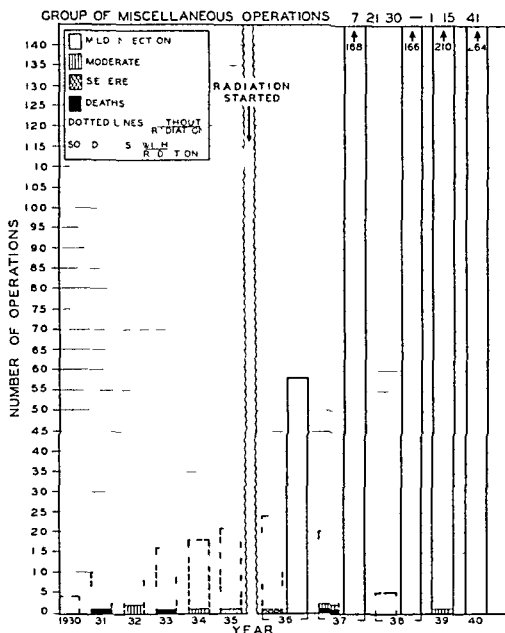


CHART 10—This chart includes all operations performed with radiation and not included in Charts 4-9. It is given in order to make a complete presentation of our operative experience with the use of air sterilization. See text for more complete analysis.

MISCELLANEOUS OPERATIONS—CHART 10

Beginning shortly after the installation of the first radiation unit an increasing number of miscellaneous operations (Chart 10) not included in Charts 4-9, inclusive, have been performed in such a field of sterile air. They include a wide variety of operations in general—thoracic, plastic, and urologic surgery—and this chart serves, primarily, to complete the presentation of the total number of operations performed in a field of ultraviolet radiations. It also shows the improvement in this heterogeneous group of operations brought about by the use of air sterilization, even though their diverse types make comparisons somewhat less valuable.

The cases without radiation that were analyzed include only splenectomies, certain other celiotomies where the hollow viscera were not opened, nerve sutures, excision of benign breast tumors, and certain other tumors over the body. Also in this group are the remaining three deaths from infections listed on Chart 3, and not included in the operations shown on Charts 4-9, inclusive. Other types of these miscellaneous operations performed without radiation were not analyzed because there was not a sufficient number of any one type to give statistics which could be evaluated or compared.

The radiated group in this chart is more diverse, since every operation performed in a field of bactericidal radiation and not included in one of the other charts is listed here. Slightly less than 200 of these were potentially infected at the time of the operation. All operations with radiation are included in the columns indicating the totals, but every potentially infected case both with and without radiation was ruled out in the analysis for infections in clean operations as indicated by the shaded area. After eliminating these potentially infected operations, there were between 600 and 700 miscellaneous clean operations performed in a field of ultraviolet radiation, with only one infection.

This infection with the hemolytic staphylococcus aureus followed a four-hour operation for removal of a cystic hygroma of the neck, during the course of which the submaxillary gland was cut across. It may have resulted from cutting across the salivary gland, from lymphatic drainage from the mouth or respiratory passages, from skin contaminants, or may have originated from contaminants reaching the wound from outside the body, such as from the air or from some other unexplained source.

INFECTING ORGANISMS

Ninety-one per cent of the organisms causing the infections reported in this survey both in the fatal and nonfatal cases, with and without radiation, were staphylococci, while 83 per cent of all offending organisms were hemolytic or nonhemolytic staphylococcus aureus (Table I). Many of the organisms reported as *Staphylococcus aureus* were undoubtedly hemolytic, as the laboratory did not always report on hemolysis. In general, the more severe infections were caused by the hemolytic staphylococcus aureus or by a combination of a hemolytic streptococcus with the *Staphylococcus aureus* or colon bacillus, with the exception that in certain brain operations, organisms of relatively low virulence at times produced a fatal meningitis (Chart 3).

Of the 142 positively identified organisms, 127 were from 207* infected wounds in the 1,735 large clean operations performed without radiation, and eight were from the nine infected wounds among the 140 reopened thoracoplasty wounds where radiation was used. Only seven were from six mild

* Many orthopedic patients were discharged in a plaster encasement, without a culture having been taken, and the infection was diagnosed without a culture from the draining wound described in the follow-up clinic, in certain other cases a culture was taken but the report was not recorded, while in some mild or moderate infections there was no record of a culture having been taken.

or moderately infected wounds (two having mixed infections, and one having no growth) out of a total of 2,463+ clean primary incisions (including 283 first-stage thoracoplasties and radical mastectomies) where radiation was used (Charts 2-10 and Table I), as follows

- (1) First-stage thoracoplasty, with excision of an enlarged lymph node during mobilization of the apex (Chart 4)
- (2) Triple arthrodesis of the ankle, with a large slough of the skin flaps (Chart 6)
- (3) Open reduction—comminuted fracture patella—where test was not obtained (Chart 6)
- (4) Cerebellar exploration—probably started as a stitch abscess (Chart 7)
- (5) Excision of hygroma neck, with cutting across lymphatics and submaxillary gland (Chart 10)

Out of this total of 142 positively identified organisms in wounds, either in pure or mixed culture, the *Beta* hemolytic streptococcus was present only seven times, or 5 per cent of the total (Table I). Six of these seven were mixed infections (with the hemolytic staphylococcus aureus in two, the *Staphylococcus aureus* [no note as to hemolysis] in three, and the colon bacillus in one, the only pure culture being from an hematoma, with a mild infection). Four of the seven wounds infected with hemolytic streptococci were on the Orthopedic Division* and three of the four patients so infected died as a result. The only death from a streptococcal wound infection, other than on the Orthopedic Service, was from peritonitis following biopsy of a retroperitoneal lymph node during a celiotomy for an inoperable carcinoma of the stomach. This infection, in a debilitated patient (Chart 3—March 21, 1931), may have followed cutting across infected lymphatics.

Thus, four, or 21 per cent, of the 19 patients who died of an "unexplained" operative or postoperative infection (Chart 3) showed the *Beta* hemolytic streptococcus in their wound, but in none of the four was it present in pure culture. However, the two of these four patients with a proven septicemia did show the *Beta* hemolytic streptococcus in pure culture in their blood. Thus, even though this organism was present, usually as a mixed infection, in only 5 per cent of the total infections, it was present and played an important rôle in 21 per cent of the deaths from infection. We are unable to make any statement as to whether or not the combination of organisms increased the severity of these streptococcal infections, but it seems quite likely that it did.

Undoubtedly, when the *Beta* hemolytic streptococcus is a common respiratory tract contaminant it will assume a rôle of increasing importance, insofar as wound infections are concerned. This is illustrated clearly in the report, of Walker,¹¹ from a teaching hospital in Boston, where at one time during

* This suggests the possibility of a carrier being present on that service.

the winter months the postoperative infection rate was as high as 42 per cent, with an exacerbation of streptococcal wound infections simultaneously with an increase in the streptococcal throat infections

In our experience, also, at certain periods severe operative infections are far more prevalent than at others, as illustrated by the months of November, December, and January, 1933-1934 (Chart 3). During this time, there were six deaths as a result of clean wounds becoming infected, all with the *Staphylococcus aureus* (hemolytic in four, but with no note as to hemolysis in two), but with one patient's wound also showing the *Beta* hemolytic streptococcus. Cultures revealed that a number of the personnel were persistent carriers of the hemolytic staphylococcus aureus in their nose and throat, and, at one time, approximately 80 per cent of the general population and of the operating room personnel were either transient or persistent carriers of the hemolytic or nonhemolytic staphylococcus aureus in their respiratory passages. During other years, the percentage of positive cultures of these organisms from the nose and throat has remained far below this level.

Of the 19 patients dying from infection in a clean wound, in none of which radiation was used (Chart 3), only five (four with brain operations and one with an orthopedic operation) failed to show the *Staphylococcus aureus* in their wound, and one of these showed, on the smear gram-positive cocci in clumps—probably staphylococci—but the culture was overgrown with *B. proteus* and this organism was not positively identified. Eleven of the patients who died (including three of the seven patients dying of meningitis following a brain operation) had their wound infected with the *Staphylococcus aureus* in pure culture. In nine of these, it was definitely stated that the organism was hemolytic, while in two there was no note as to hemolysis (Chart 3). In neurosurgery, death from meningitis may be caused by less virulent organisms, which in the usual wound would at most cause only a trivial or moderate infection. This is illustrated by the four deaths from meningitis, caused by the *Staphylococcus albus* in two cases, a gram-positive diplococcus in one case, and by an unidentified gram-positive coccus in clumps in one case (Chart 3). All other deaths from infection were caused by the *Staphylococcus aureus*, usually hemolytic, or the hemolytic streptococcus, or a combination of organisms, in which one or both of these played a part.

Where radiation was used, there has been no severe or fatal "unexplained" wound infection in any clean primary incision or reopened wound. The six infections, or 0.24 per cent, some of questionable origin, that occurred were caused by *Staphylococcus aureus* or *albus* in all cases, except one orthopedic operation where there was a mixed infection with the *Beta* hemolytic streptococcus and hemolytic staphylococcus aureus. The latter infection may have occurred in the operating room but it may not have developed had not there been a large skin slough (Chart 6). It is interesting to note that this is the only orthopedic patient in this report infected with this combination of organisms who did not die as a result of the infection.

TABLE I
ORGANISMS CAUSING INFECTION IN CLEAN WOUNDS (7/21/30-1/15/41)

Organism	Without Radiation		With Radiation		
	All Wounds	Wounds with Fatal Infection	Primary Incision	Reopened Wounds	Deaths from Infection
Hem staph aureus	54	9	2	3	0
Staph aureus*	44	2	2	3	0
(Staph aureus)					
(B hem strep)	3	3	0	0	0
(Hem staph aureus)					
(B hem strep)	1	0	1	0	0
Staph albus	0	2	1	2	0
B hem strep	1	0	0	0	0
(B hem strep)					
(B coli communior)	1	1	0	0	0
Colon bacillus	3	0	0	0	0
Proteus overgrowth	2	1	0	0	0
B subtilis	2	0	0	0	0
B pyocyaneus	1	0	0	0	0
Gram pos diplococci	1	1	0	0	0
Total organisms	127	23	7	8	0

* This group contains all organisms where there was no note as to hemolysis. Since the cultures were made by interns rotating through the laboratory and they at times did not differentiate between hemolytic and nonhemolytic staphylococci undoubtedly a number of these organisms were hemolytic.

Ninety-one per cent of all positive cultures showed a staphylococcus, with the *Staphylococcus aureus* (hemolytic or nonhemolytic) in 83 per cent. Five of the wounds (3.6 per cent of the total with positive culture) showing *Staphylococcus aureus* also contained the *Beta* hemolytic streptococcus. The latter organism was present only seven times (5.1 per cent of all infected wounds), on only one occasion in pure culture (a mild infection in an inguinal hernia), while the mixed infections showed, in addition, staphylococci in five, and colon bacilli in one. Four of these six mixed infections resulted in the death of the patient (Chart 3). With the exception of brain operations where an organism of relatively low virulence may cause death from meningitis, all fatal infections were caused by the hemolytic staphylococcus aureus or the *Beta* hemolytic streptococcus either singly or as part of a mixed infection. A combination of these two organisms seemed to be particularly virulent (Chart 3).

SUMMARY AND CONCLUSIONS

(1) In evaluating air sterilization as an addition to "aseptic operating room technic," selected groups of large clean operations (all thoracoplasties, radical mastectomies, herniorrhaphies, thyroidectomies, orthopedic, and neurosurgical operations), some of each group performed with and others without radiation, as given in the charts, and covering a period of ten and one-half years, were analyzed for unexplained infections.

The operations analyzed can be divided into two groups:

- (I) 1,313 out of a total of 15,674 performed before radiation was instituted—a period of five and one-half years, and

- (II) 3,272 (469 without radiation and 2,803 with radiation) out of a total of 30,695, performed after radiation was instituted—a period of five years

As a further check on the value of bactericidal radiation the records of all patients dying following any type of operation (approximately 700 were analyzed to determine the number of deaths from “unexplained” infections in clean wounds) Out of the first group of 15,674 operations, before radiation was instituted, there were 17 deaths from “unexplained” infections (Charts 1 and 3), while out of the second group of 30,695 operations, after radiation was instituted, there have been only two deaths from “unexplained” infection where radiation was not used and no such death where radiation was used (Charts 1 and 3) During this last period most of the large wounds likely to develop a severe infection have been protected from air contaminants during operation by bactericidal radiation

(3) The air in the operating room is contaminated by the occupants who carry pathogenic organisms in their noses and throats¹³

(4) The generally accepted operating room mask will prevent massive droplet infection, but will not prevent the nose and throat contaminants from being given off into the air in finer particles

(5) Fatal “unexplained” wound infections in the Duke Hospital have occurred only during the months when the air contamination and respiratory tract infections were likely to be high (Chart 3)

(6) Severe “unexplained” operating room infections may reach epidemic proportions at rare intervals (Chart 3)

(7) The degree of air contamination can be reduced by supplying large quantities of clean air which is not recirculated, or by sterilizing recirculated air in the ducts, but recontamination of the air by the occupants of the room prevents a reduction in the bacterial level by these measures to a point adequate for the prevention of wound infection

(8) After a most detailed analysis of the conditions in our operating rooms, covering a period of several years, we were forced to the conclusion that the pathogenic bacteria, given off from the respiratory passages of the occupants, and floating in the air, constituted the greatest hazard of infection in a clean wound in the modern well-run operating room

(9) As an experimental project to prove or disprove the conclusions given in the preceding paragraph (8), we adopted air sterilization by ultraviolet radiation (over 85 per cent at 2537Å) of an intensity throughout the entire room adequate to reduce the sedimenting viable bacteria at the operative site (including the sterile supplies) to 1–2 colonies per Petri dish, per hour of exposure

Although many things may be done to reduce the air contamination, we have as yet found no method that is as adequate or as simple as continuous exposure of the air to this bactericidal radiation

Attention must be kept centered on the importance of air contamination

in the operating room and not diverted to the particular method of controlling it

(10) Sterilization of the air by radiation resulted in the following reduction in the "unexplained" infections (Table II)

TABLE II

	Without Radiation	With Radiation
Thoracoplasties first stage, and radical mastectomies	32%	to 0 35%
Orthopedic operations	16 5%	to 0 74%
Neurosurgical operations	9%	to 0 22%
Herniorrhaphies	8 3%	to 0 00%
Partial thyroidectomies	1 8%	to 0 00%

(11) The death rate from "unexplained" infections in these large clean operations reported, was reduced from 1 07 per cent in 1,735 operations performed with the generally accepted methods of protecting the wounds during operation from nose and throat contaminants, to zero per cent in 2,463+ operations performed with the wound protected during operation by sterilization of the air with ultraviolet radiation

(12) Reopened wounds are more likely than primary incisions to become infected from sources other than the air

(13) In the North Carolina Sanatorium, at Sanatorium, N C, the percentage of thoracoplasty wounds (all stages) having severe infections was reduced from 22 7 per cent in 75 consecutive operations without radiation to 1 09 per cent for the next 92 operations which were performed with bactericidal radiation. The only operating room infection in the latter group was in a wound reopened for the second stage (compare with Charts 4 and 5)

(14) The pathogenic bacteria most commonly encountered in this ten and one-half-year period of study covering wound infections, air contamination, and the nose and throat flora, have been *Staphylococcus aureus*, both hemolytic and nonhemolytic (Chart 3 and Table I)

Hemolytic streptococci, while rarely encountered in this analysis (5 per cent of the total identified organisms obtained from wounds), have usually occurred in combination with other organisms, predominantly *Staphylococcus aureus* (Chart 3 and Table I), and have caused the death of 57 per cent (four out of seven) of the patients so infected. Even though infections with the hemolytic streptococcus in our experience have been rare, under conditions of widespread nose and throat contamination with this organism, it can become a major threat in any operating room if air transportation of bacteria is ignored

(15) In wounds protected from air contaminants during operation by sterilization of the air with ultraviolet radiation, any type of "unexplained" infection in a clean wound was extremely rare and never severe. This indicates that the organisms were present in smaller numbers, were attenuated or less virulent, gained access to only a localized part of the wound, or that

the wound itself had an increased resistance to the infection (Charts 3-10 and Table I)

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BOOK REVIEWS

TEXTBOOK OF SURGERY By JOHN HOMANS, M D, Fifth Edition Springfield, Ill
Charles C Thomas Co, 1940

IN THE PREFACE to the First Edition of Homan's Surgery, the author credits Dr Harvey Cushing with inspiring him to record and amplify lectures then given by members of the Surgical Department of the Harvard Medical School, and to put into writing within a single volume the history, the fundamentals, and something of the practice of surgery. The immediate success of his first edition was evidence that he accomplished these aims, and a second edition followed within a year. The present volume completes the fifth, published in less than nine years. This is a record that should be enough to satisfy even the present generation of undergraduate medical students, and it certainly is an unusual achievement for an author at the present time.

To attempt to review in detail the text of this last edition would be like "painting the lily." As in all former editions, it makes delightful reading, and to the reviewer, no higher compliment could be received than a recent statement of a medical student "It reads like a novel."

WALTER ESTELL LEE, M D

PUBLICATIONS FROM THE DIVISION OF SURGERY OF THE NORTHWESTERN UNIVERSITY
MEDICAL SCHOOL Chicago 1940

THE PUBLICATIONS during 1939 of the Division of Surgery of the Northwestern University Medical School have been collected and published as Volume 6.

These papers have all appeared in various medical and surgical journals during the year, and as they are not indexed in this volume, nor are they arranged in such a way as to facilitate their use for reference, it is evidently the intention of the editors that the papers will be consulted and referred to as indexed in the Index Medicus and the Quarterly Index.

The 44 papers cover many subjects, including Technic, Pre- and Postoperative Care, Water and Electrolyte Balance, Chemotherapy, Diseases, Congenital Anomalies, Trauma, Malignancies of Special Organs, and many Systems, and they represent productive effort of which the Medical School has reason to be proud.

WALTER ESTELL LEE, M D

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BLOOD TRANSFUSION REACTIONS THEIR CAUSES AND PREVENTION

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CHICAGO, ILL

FROM THE TRANSFUSION DEPARTMENT AND THE DEPARTMENT OF SURGERY, MICHAEL REESE HOSPITAL CHICAGO ILL

THE LAST FEW YEARS have seen a tremendous increase in the use of blood transfusion, the fruition of three centuries of experiment and effort to treat disease by the administration of blood. The present-day, widespread use of this therapeutic measure coincides with the perfection of indirect methods of transfusion and the demonstration that these methods are eminently safe. Growing out from the indirect transfusion have come preserved blood transfusions and the transfusions of serum and plasma, all of which have greatly extended the scope and indications of blood transfusion. This vast increase in the numbers of transfusions given constitutes a challenge to reduce the incidence of untoward reactions to the lowest possible figures. Experience has shown that the causes of posttransfusion reaction are not inherent in the indirect methods, and that the control of such reactions demands centralized responsibility over all of the component steps of the transfusion operation, careful supervision of the numerous individual potential sources of error, and everlasting alertness to trace and eliminate breaks in technic. The purpose of this paper is to record the evolution of the present blood transfusion set-up at Michael Reese Hospital, tracing the gradual reduction of transfusion reactions, and to describe a modern blood transfusion department for a general hospital.

Organization of a Blood Transfusion Department—The first requirement in establishing an adequate blood transfusion service is the creation of a definite department in which all of the phases of the operation are centralized, and under unified responsibility and control. If the typings and serologic examinations are done in one department, the cleansing and sterilization of

equipment in another, the drawing of blood in a third, to say nothing of the preparation of solutions, distillation of water, testing for the presence of pyrogenic substances, maintenance of donor lists, and keeping of records, it is obviously impossible to place responsibility for the occurrence of reactions, or to trace them to their source when they do appear.

The Blood Transfusion Department was established at Michael Reese Hospital in September, 1939. Separate quarters were allotted for this important work, and full-time personnel were assigned to carry out the various procedures incident to transfusions. The whole was placed under the direct and sole responsibility of the Director of the Serum and Transfusion Centers.

The Department continues to function as constituted with increasing satisfaction. All phases of the effort connected with the transfusion of blood, other than its actual injection, are performed in the Center. Here the blood groupings and compatibilities are determined, the Wassermann and Kahn tests made, and the other necessary laboratory examinations carried out. Professional donor lists are maintained and kept up to date, prospective donors are subjected to careful physical and hematologic examination, and family donors are selected and tested. All equipment for both the withdrawal and administration of blood is cleansed, assembled, wrapped, and sterilized in the Center. An adequate system of checks and cross-checks has been adopted to avoid infusing the blood into the wrong patient. If repeated reactions occur, an immediate reinvestigation of the entire procedure is made, with the aid of pyrogen tests, until the cause is found and eliminated.

Examination of Professional Donors—Rigid requirements must be fulfilled before a person can be registered as a professional donor. Only healthy young males with good veins are selected. A careful history is taken of each candidate to rule out allergy, tuberculosis, malaria, and syphilis. A complete physical examination is then made. This includes a Wassermann and Kahn test, complete blood count, and differential blood smear examinations. Syphilis, secondary anemias, blood dyscrasias, and malaria are thus ruled out.

No professional donor is used more often than once in six weeks. The serologic tests are repeated every six weeks. In addition, the genitalia and the oral cavity are inspected immediately before blood is drawn for transfusion, in order to rule out recent syphilitic infections in which the serologic tests have not yet become positive.

Active donor lists comprising the various blood groups are maintained at all times. Prospective donors must remain on call, and within 20 minutes' reach of the hospital. Blood can thus be delivered to the patient within 30 minutes from the time the call is received in the Transfusion Center.

Examination of Family Donors—Family donors who wish to provide blood are typed in the Transfusion Department and, if their blood group is found suitable, cross-compatibility tests are made. An immediate Kahn test is then done on the serum of the prospective donor. Family donors are obviously less amenable to the rigid control exerted over professional blood donors. It is not feasible to take a complete history, or to do a careful

physical and hematologic examination Even the inspection of the genitalia and oral cavity is sometimes resented These considerations, plus the time consumed in making the Kahn test, which takes about an hour, make family donors less desirable than professional ones aside, of course, from the economic factors

Methods of Typing—It goes without saying that careful blood group determinations are made upon all prospective patients and donors Emphasis is placed upon the use of high-titer testing sera, to obviate the possibility of overlooking faint agglutinations, which may occur with low-titer sera The International classification of the blood groups (Landsteiner) is used rather than that of Jansky or Moss, so that there will be no room for doubt or misunderstanding The four groups, according to the International classification, are designated O, A, B, and AB, on the basis of the presence or absence of agglutinogens in the cells

In addition to the blood typings, direct compatibility tests are made before each transfusion, matching and cross-matching the blood of the donor with that of the patient These tests require very little additional time, and contribute materially to the safety of the transfusion By rejecting all bloods that give the faintest question as to compatibility, the dangers of subgroup agglutination can be avoided

Collection of Blood—We are now using commercially prepared vacuum bottles exclusively for the collection of blood for transfusion These bottles are hermetically sealed, and contain pyrogen-free 2.5 per cent sodium citrate in physiologic saline solution A large-bore needle, equipped with a metal valve for regulating the rate of flow, is plunged through the stopper, into the bottle Attached to the valve is a short length of rubber tubing which is armed with a No. 16-gauge blood-letting needle With this apparatus, the procedure of drawing blood is exceedingly simple, and can be done by one person, unaided The needle is introduced into the vein of the donor, the valve is opened slightly, and the blood is drawn by suction into the closed bottle When the desired amount has been obtained, the needle is withdrawn from the arm, the valve-bearing needle is removed from the stopper, and a sealed, sterile flask of citrated blood is ready for administration or storage, as may be desired

The administration of the blood is not a function of the Transfusion Center The flask, properly prepared and labeled, is turned over to the clinical staff for injection The technic thereof is equally simple Another needle pierces the stopper, and is attached to an infusion set which is equipped with a fine-gauge metal filter and a drip-chamber The bottle is inverted, the needle inserted into the vein of the patient, and the blood is given by the drip method in a manner similar to that of any intravenous infusion The blood is, at all times during the procedure, kept in a closed system, and is not exposed to any or external sources of contamination, thereby minimizing greatly the potential causes of posttransfusion reaction

Cleansing of Equipment—Pyrogen Tests—It is now recognized that most

reactions are of the pyrogenic type, and that these are almost invariably due to the presence of contaminants in the apparatus or solutions. Proper cleansing of all parts of the equipment used is, therefore, of paramount importance in controlling transfusion reactions.⁹ The glass and metal parts are cleansed relatively easily by washing in an acid solution, followed by distilled water. Care of rubber tubing is more difficult. In order to remove soluble pyrogens, it is necessary to boil the tubing first in a weak solution (0.1 to 0.2 per cent) of sodium hydroxide, and then in distilled water.

In order to be sure that no injurious foreign material remains in the tubing, a sample of the final washings in each batch is subjected to a *pyrogen test*. This consists of injecting an isotonic and sterile quantity of this material into the ear-vein of a rabbit. If pyrogenic substances are present, the animal will exhibit a typical pyrogenic reaction, with fever and, possibly, chills.

When the equipment has been proved to be satisfactorily clean, it is wrapped and autoclaved, and is then ready for use. Records are kept of all rubber tubing used, including the date of its preparation and the results of the pyrogen test. This facilitates checking back if reactions are reported.

Storage of Blood—Most of the blood transfused at Michael Reese Hospital is administered immediately, or within a few hours after collection. While there are certain advantages in the use of stored blood, particularly in urgent cases, where the time factor is so important, there are also comparable objections due to the rapid disintegration of leukocytes, platelets and prothrombin, and to the shorter survival period of the stored red cells.^{1, 7, 13} Other things being equal, we prefer the use of fresh blood, but a stock of refrigerated and citrated blood is kept on hand for emergency use.

It has been our policy to store blood for not longer than three days. If it is not used within that period, the plasma is drawn off under sterile conditions and pooled, to be used for plasma transfusions. When stored blood is used, no attempt is made to warm the refrigerated blood before injection because it has been shown that the administration of blood at low temperatures is not injurious, whereas the artificial heating of blood increases the risk of hemolysis.^{2, 4}

Methods of Keeping Transfusion Records—The importance of keeping detailed records of every transfusion cannot be too strongly emphasized. If the entire clinical situation surrounding the administration of blood is tabulated in a systematic manner, it becomes rather easy to trace the factors contributing to a posttransfusion reaction. The records are filed chronologically, with a cross-index arranged alphabetically (patients' names), as well as according to diagnosis or indication for transfusion. This information is acquired from several sources, including an abstract of the patient's chart, reports from interns and nurses, and by follow-up by the Transfusion Department. If a severe reaction is reported, a posttransfusion specimen of urine is examined for the presence of hemoglobin, and the clinical findings are correlated and compared with the pretransfusion course of the patient. The transfusion record chart used is herewith reproduced.

BLOOD TRANSFUSION REACTIONS

TRANSFUSION RECORD

Drawn

Given

Donor

Name

Address

Tel

Age

Sex

Wgt

Phys

Cond

Rbc

Hgb

History

Recipient

Name

Address

Tel

Age

Sex

Wgt

Type

Allergy

Disease

Duration

Blood

Days Preserved

Type

Compatibility

Amount

Sterility

Kahn

Wassermann

Solutions added

Administration

Duration

Smoothness of flow

Amount actually given

Remarks

EFFECTS (including preceding 48 hours)					
Date	48-24 H before	24-0 H before	0-24 H after	24-48 H after	48-72 H after
R B C					
H G B					
T (max)					
T (min)					
P					
R					
B P					
Chills					
Cyanosis					
Gen Cond					
Urine					
Ashby Count					
Remarks					

BLOOD TRANSFUSION REACTIONS

Blood transfusion reactions may be classified simply as (1) pyrogenic or febrile, (2) allergic, and (3) hemolytic. Of these, the most frequent by far are the pyrogenic reactions. These consist essentially of a chill coming on during or shortly after the transfusion, followed by a sharp rise in temperature, which returns to normal within 24 or 48 hours. We consider a major pyrogenic reaction one in which there is a rise in temperature of at least two degrees above the pretransfusion level. If the temperature elevation is less than two degrees, it is considered a minor reaction. Pyrogenic reactions are not followed by jaundice, urinary retention, or hemoglobinuria. These phenomena indicate an incompatibility or hemolytic reaction. While the pyrogenic reaction is of itself not dangerous, the added load it imposes upon patients already critically ill cannot be disregarded.

Pyrogenic reactions are caused, almost invariably, by the inadvertent injection of foreign protein matter with the blood. Such foreign material may be present in any part of the transfusion apparatus, and particularly in the rubber tubing. A frequent source of febrile reaction is the water from which

the solutions are made, or that which is used for the final irrigation of the apparatus¹¹ If, in the process of distillation, such fluids are incompletely freed from pyrogenic material, febrile reactions will ensue Similar reactions are frequently seen following infusions of saline or glucose solutions which contain protein contaminants In evaluating the source of posttransfusion reactions, therefore, it is important to know whether such fluids, if given, contained pyrogenic substances

Allergic reactions following transfusions of blood usually manifest themselves in the form of urticaria, occasionally by asthma or other visceral disturbances Such reactions are readily controlled, as a rule, by the administration of adrenalin and are included, therefore, with the minor reactions They are seen at times when a patient receives blood from the same donor for a second or third time, or when the donor has a history of allergic sensitivity Occasionally, such reactions can be traced to blood drawn shortly after the donor has eaten To reduce the incidence of this type of reaction, it would appear that allergic persons should not be taken as blood donors and that, whenever possible, blood should be drawn during the fasting state However, allergic symptoms are frequently seen following transfusions where neither the patient nor donor have been known to have allergic tendencies

Hemolytic reactions are extremely uncommon, fortunately, since the general adoption of careful and accurate blood typing and cross-matching Such reactions are usually due to incompatibility of the bloods, although occasionally overheating or prolonged storage of blood may cause sufficient destruction of red cells to cause a hemolytic reaction The clinical manifestations of such reactions are severe lumbar pain, dyspnea, cough, chills, and varying degrees of collapse, followed by jaundice and hemoglobinuria These may lead to complete anuria and death from uremia If diuresis can be effected, recovery usually ensues The severity of hemolytic reactions is proportional to the amount of erythrocytic destruction in the infused blood

Analysis of Records of 2,500 Transfusions—In order to determine the actual incidence of blood transfusion reactions, and to compare the incidence following successive changes in technic, we have studied five series of 500 transfusions each Prior to 1937, direct transfusions were administered routinely at the hospital The technic used was the Strauss¹² modification of the Lindeman method, in which multiple large syringes are alternately filled with blood from the donor and immediately discharged into the vein of the recipient The first series consists of 500 consecutive transfusions done by this method

During the year 1937, citrate transfusions were reintroduced into the hospital and, almost overnight, there was a general and spontaneous adoption of this method The original Lewisohn technic was employed, wherein the blood is collected into an open flask or beaker containing citrate solution, and is infused by gravity through a funnel, with several thicknesses of gauze for a filter The second series of transfusions was drawn from this period

The third series of cases dates from 1939, and represents the early experi-

ences with the revised technic in the new Transfusion Department. The fourth series of 500 transfusions were taken from the second year of the activities of the Transfusion Center after the elimination, one by one, of a number of sources of transfusion reactions. The final series of 500 transfusions were given during a ten-week period in the spring of 1941, and represent the current status of transfusion effects.

RESULTS—The change in transfusion technic from the direct to the citrate blood method was reflected in an immediate and striking increase in the number of transfusions given. Prior to 1937, an average of 500 transfusions were given annually in the hospital. At the present time, thanks to the greater ease and facility of the citrate method, the number has risen to 2,500 transfusions per year. The cases studied in this report obviously do not represent all of the transfusions given during the period covered, but are sample batches of unselected, consecutive series numbering 500 each, drawn during successive stages in the evolution of our present transfusion program.

Incidence of Reactions—Our investigations indicate a progressive reduction in the incidence of blood transfusion reactions in the five successive series of transfusions studied (Table I). The direct transfusions gave a surprisingly high incidence of reactions, when subjected to actual statistical analysis. Febrile reactions contributed the greatest number. They were noted in 7.7 per cent of the transfusions, and in 5 per cent they were of major severity. In retrospect, this high incidence of pyrogenic reactions is not surprising. The importance of the utmost care in eliminating foreign material from all equipment and solutions was not thoroughly appreciated. The syringes and tubing were not given the special attention now considered essential in preparing transfusion equipment. During the transfusion, the syringes were rinsed in open basins containing citrate solution, distilled water and salt solution, the manufacture of which was done in a routine manner. It is a tribute to the method, which permitted but limited contact of blood with foreign surfaces, that the incidence of reactions was not higher.

Series II, comprising a sample of 500 consecutive citrated blood transfusions done by the open method showed, surprisingly, a slightly lower incidence of reactions than did the direct method. In this group there were a total of 7.4 per cent reactions, with pyrogenic disturbances in 7 per cent. Of these, 6 per cent were classed as major reactions. The manifold potential sources of contamination with pyrogen-containing substances are obvious. Nevertheless, there was probably less contact of the equipment with impure solutions, which is reflected in the slightly lower incidence of febrile reactions.

The third series of transfusions comprised the first 500 given under the present set-up. The results were somewhat disappointing. Although there was some reduction in the number of reactions, this was not as striking as had been expected. The total reaction rate was 7.2 per cent, of which 5.2 per cent were pyrogenic and, of these, 3.8 per cent were of major severity. However, the system of adequate record keeping, and the use of the pyrogen test to detect the source of contamination, permitted a progressive elimination of

the various factors responsible for reaction, with gradually diminishing incidence of untoward effects

The importance of these measures is demonstrated by the figures presented by Series IV. A striking fall in the incidence of pyrogenic reactions is seen, to 2.8 per cent, of which only 1.6 per cent are classed as major reactions. This represents a reduction to approximately 50 per cent of the previous series. The last series, indicative of our present rate of reactions, is encouraging indeed. The total number of reactions amounted to slightly over 2 per cent, with only 0.6 per cent of major pyrogenic disturbances. With continued alertness and further improvements in technic, even better results are to be anticipated.

TABLE I
INCIDENCE OF REACTIONS FOLLOWING TRANSFUSIONS

	Pyrogenic Reactions			Allergic Reactions	Hemolytic Reactions	Total Reactions
	Major	Minor	Total			
<i>Series I</i>						
500 Consecutive Direct Transfusions (multiple syringe) 1936	25 (5.0%)	14 (2.8%)	39 (7.8%)	9 (1.8%)	0	48 (9.6%)
<i>Series II</i>						
500 Consecutive Indirect Transfusions (open method) 1938	30 (6.0%)	5 (1.0%)	35 (7.0%)	2 (0.4%)	0	37 (7.4%)
<i>Series III</i>						
500 Consecutive Indirect Transfusions (early new method) 1939	19 (3.8%)	7 (1.4%)	26 (5.2%)	10 (2.0%)	0	36 (7.2%)
<i>Series IV</i>						
500 Consecutive Indirect Transfusions (recent new method) 1940	8 (1.6%)	6 (1.2%)	14 (2.8%)	5 (1.0%)	0	19 (3.8%)
<i>Series V</i>						
500 Consecutive Indirect Transfusions (Feb. to May 1941)	3 (0.6%)	8 (1.6%)	11 (2.2%)	4 (0.8%)	0	15 (3.0%)

In all of the cases presented here, the blood transfusions were charged with a certain number of reactions for which they were not really responsible. Most patients who are ill enough to require blood transfusions also receive infusions of salt and glucose solutions. As has been indicated, such infusion liquids are as capable of inducing febrile reactions as are blood transfusions, if pyrogenic contaminants are present. Recently, commercial infusion liquids have been adopted for routine use in the hospital, and the preparation of the tubing and needles has been subjected to the same care and supervision as is employed with transfusion equipment. This should be reflected, not only in a lower incidence of infusion reactions, but also in the number of reactions attributed to blood transfusions.

In an attempt to further analyze the causes of transfusion reactions, these were correlated with the diseases for which the transfusion was administered. In a study of 1,000 consecutive transfusions, (Table II) pyrogenic reactions were encountered most frequently in patients suffering from various types of blood dyscrasias, including leukemias, thrombocytopenic purpuras, hemolytic anemias, etc. This observation has been made by others.⁸ Furthermore,

BLOOD TRANSFUSION REACTIONS

pyrogenic reactions were more frequently seen in febrile than in afebrile patients. It appears that patients suffering from septic diseases are particularly sensitive and responsive to minute and otherwise innocuous amounts of pyrogenic material. In these patients, chill reactions could be reduced in frequency and severity by the administration of multiple small transfusions, not exceeding 250 cc of blood at a time. This presumably reduces the quantity of pyrogenic substance sufficiently to prevent reaction even in a sensitive patient.

This predisposition on the parts of septic patients to sustain reactions may explain, in part, the higher incidence of reactions on the medical services than on the surgical services. Within the surgical group, pyrogenic reactions occurred more frequently in patients treated for gynecologic disorders than in any others. In 29 patients of the "clean" Orthopedic Service, who were transfused during or after orthopedic operations, not a single untoward reaction occurred. The series, however, is too small to warrant drawing definite conclusions.

TABLE II
THE INCIDENCE OF TRANSFUSION REACTIONS IN PATIENTS CLASSIFIED
ACCORDING TO DIAGNOSIS AND DEPARTMENT

	No of Trans- fusions	Pyrogenic Reactions	Per Cent	Allergic Reactions	Per Cent	Total Reactions	Per Cent
Surgical Patients							
Gynec surgery	56	4	7.1	1	1.8	5	8.9
Orthoped surgery	29	0	0.0	0	0.0	0	0.0
All other surg depts	415	10	2.4	3	0.7	13	3.1
Medical Patients							
Blood dyscrasias	45	8	17.7	0	0.0	8	17.7
Ulcerative colitis	50	1	2.0	5	10.0	6	12.0
All other medical diseases	340	13	3.8	5	1.4	18	5.2
Obstetrics	65	4	6.1	1	1.5	5	7.6
Totals	1 000	40	4.0	15	1.5	55	5.5

An interesting finding was the fact that reactions seemed to occur in aggregates of four or five within a day or two, followed by no reactions for perhaps two or three weeks. Invariably, we were able to trace the causes for these reactions and, in most cases, to remedy the cause. On one occasion, it was a batch of new tubing that had been inadequately prepared. Another time the salt solution contained pyrogenic impurities, and in a recent occurrence of chill reactions, it was found that particles of old blood were left behind because the metal valves were not taken apart in the course of cleansing. The important point is that, by virtue of the accurate record system, it was relatively easy to trace the various sources of contamination.

It will be noted from the tables that no hemolytic reactions were encountered in the entire series of transfusions reported. Freedom from this, the most dangerous type of posttransfusion reaction, is attributed to the carefulness of the preliminary typing and compatibility tests. By using only high-titer testing sera and by rejecting all bloods giving a questionable agglutination, the dangers of subgroup agglutinations can be avoided. Reciprocal

cross-matching of both serum and cells of recipient and donor further protects the patient from receiving incompatible blood

The Use of Universal Donors—Several investigators^{6, 10, 13} have shown that infusion of blood from universal donors (Group O) into patients of other blood groups may result in hemolytic reactions. The use of universal donor-blood is considered especially dangerous if the agglutinin titer of the donor's serum against the recipient's cells is 1:32 or higher, and if more than 200 cc of blood of this type is used.

In our series of 1,000 recent transfusions studied, universal donor-blood was given to patients of other blood groups 220 times. The percentage of untoward reactions was actually lower in these cases than in the other 780 in which recipient and donor belonged to the same blood group. According to Wiener¹³ such statistics have not been previously recorded. No hemolytic reactions were encountered, regardless of the agglutinin titer of the donor's serum. In most instances, 500 cc of blood was given. We believe, therefore, that it is safe to administer universal donor-blood to patients of other blood groups, provided, by the use of high-titer typing sera, the correct group classification of the donor is assured. Careful direct compatibility tests between recipients' and donors' bloods must be performed before every transfusion to rule out the presence of anti-O agglutinins in the recipients' serum.¹⁴ The same principles should apply to the transfusion of other blood group bloods to universal recipients.

TABLE III

INCIDENCE OF REACTIONS IN PATIENTS TRANSFUSED WITH BLOOD OF THE SAME TYPE AND IN THOSE RECEIVING BLOOD OF A DIFFERENT TYPE (UNIVERSAL DONOR BLOOD)

	Number of Transfusions	Pyrogenic Reactions	Allergic Reactions	Total Reactions
Patients and donors of same blood group	780	35 (4.5%)	12 (1.5%)	47 (6.0%)
Patients and donors of different blood group	220	5 (2.2%)	3 (1.4%)	8 (3.6%)
Totals	1 000	40 (4.0%)	15 (1.5%)	55 (5.5%)

SUMMARY AND CONCLUSIONS

(1) The control of blood transfusion reactions demands centralized responsibility over all of the component steps of the operation, careful supervision of the numerous potential sources of error, and everlasting alertness to trace and eliminate factors causing untoward reactions.

(2) The organization of a Blood Transfusion Department for a general hospital is described.

(3) Five series of 500 transfusions each are analyzed, tracing the gradual reduction in the incidence of transfusion reactions as the various causative factors are successively eliminated.

(4) The importance of detailed records is emphasized. Complete data covering all phases preliminary to and following every transfusion make it possible to trace and eliminate the causes of reactions when they occur.

(5) The pyrogen test is an effective aid in controlling the preparation of the solutions and equipment.

(6) Reactions following transfusions are classified as pyrogenic, allergic, and hemolytic

(7) Pyrogenic reactions constitute the largest number of posttransfusion reactions. They are characterized by fever with or without chills. They are almost invariably due to the presence of foreign contaminants in the solutions or apparatus. Sepsis and blood dyscrasias predispose to pyrogenic reactions.

(8) Allergic reactions are usually urticarial in nature. The chief causes are donors with allergic tendencies and donors who have eaten shortly before giving blood. Patients with ulcerative colitis seemed to be predisposed to allergic reactions.

(9) Hemolytic reactions are usually due to the administration of incompatible blood. This can be avoided only by careful preliminary typings and reciprocal cross-matchings, the use of high-titer testing sera, and the rejection of all bloods giving questionable agglutinations. There were no hemolytic reactions in our series.

(10) Universal donor-blood gave no higher incidence of reactions than did blood of homologous groups.

(11) Our statistics reveal a reduction in the reaction incidence from 9.6 to 2.2 per cent. Only 0.6 per cent of the latter figure were major pyrogenic reactions. Our experiences point the way to the reduction of transfusion reactions, and give promise that continued improvement is to be anticipated.

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THE TREATMENT OF CERVICAL METASTATIC CANCER

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THE TREATMENT of cervical metastases is a problem which confronts every surgeon and radiologist who deals with intra-oral and pharyngeal cancer. Since the results of all methods of treatment fall so far short of a complete solution, the question of treatment must be approached open-mindedly, in its broadest aspects. In order to discuss this problem intelligently, one must first know what is meant by the term "cervical metastases." For this purpose, a few years ago, 500 consecutive cases of cervical metastases were tabulated at the Memorial Hospital according to the site of the primary lesions. These data were not taken from the clinical records but were tabulated at the time the metastases were first noted, either when the patients were admitted to the clinic or when the involved nodes were discovered at a later examination. This particular study was made only to determine the distribution of the primary sites and was not used in any of the other calculations given in this paper. The statistics are given in Table I.

TABLE I

LOCATION OF PRIMARY LESION IN 500 CONSECUTIVE CASES

Tongue	127 (25%)
Floor of mouth	44 (9%)
Extrinsic larynx	44 (9%)
Nasopharynx	40 (8%)
Lip	35 (7%)
Tonsil	34 (7%)
Mucosa of cheek	28 (6%)
Metastatic from undetermined primary	28 (6%)
Jaws	27 (5%)
Pharyngeal wall	24 (5%)
Palate	20 (4%)
Skin of face	11 (2%)
Thyroid	11 (2%)
Miscellaneous	27 (5%)
	<u>500(100%)</u>

Table I demonstrates that no single anatomic variety of intra-oral or pharyngeal cancer can be taken as representative of all cervical metastasis. It will be noted that cancer of the tongue causes 25 per cent (one in four) of all cervical metastases, and that cancer of the lip, upon which the majority of published reports concerning cervical metastases have been based, produces only one in about 15 cases, sharing only fifth place with cancer of the tonsil. A broad view of the problem of cervical metastasis, therefore, necessitates a consideration of all forms of intra-oral and pharyngeal cancer in all stages of the disease.

There is wide divergence of opinion as to the best methods of treatment for cervical metastatic cancer. Surgery and radiation both have their exponents, while some radiologists and surgeons of considerable experience doubt the

possibility of cure by any method. It is my purpose in this report to present evidence that no single treatment method is indicated exclusively, that both surgery and radiation have definite fields in the treatment of cervical metastases, and that in a considerable number of cases a combination of the two is better than either used alone. It would simplify the discussion of this proposition if the method of treatment could be selected according to a set formula, depending only upon the anatomic characteristics of the involved nodes themselves. Unfortunately, this is not possible. There are several factors relating to the primary lesion which are also of importance in the determination of the proper treatment of metastases. Although closely related, the management of the primary lesion and of the cervical metastases should be considered as separate problems, dealt with in most cases by separate procedures. I shall base my discussion on that premise, omitting any reference to the treatment of the primary lesion except as it affects the treatment of the metastases.

From the practical standpoint, the problem may be considered under two headings: (1) Prophylactic treatment, or that which is given in the absence of clinically demonstrable metastases, and (2) curative treatment given for clinically positive metastases.

Prophylactic Treatment—At the Memorial Hospital it has been the policy for the past several years to apply no prophylactic treatment of any kind to the neck in intra-oral cancer. The patients are reexamined at regular intervals, and only if and when metastases become clinically demonstrable is treatment given, and then with curative intent. The logic of such a conservative plan is based upon a statistical analysis of the subsequent clinical behavior and the eventual results in those patients who applied without cervical metastases and who were treated according to this plan.

Even though prophylactic treatment were highly efficient in dealing with clinically undemonstrable cervical metastases, nevertheless the justification for its routine use would depend also upon the percentage of cases in which it could be of actual value. It must be admitted that prophylactic treatment could be of ultimate value only in patients who apply without clinically demonstrable nodes, whose primary lesions are permanently controlled, and who then later develop cervical metastases. In other words, prophylactic treatment would be futile if the patient succumbed to an uncontrolled primary lesion or if he never developed cervical metastases in his untreated neck.

The hypothetical limit of the value of prophylactic neck dissection in cancers of the lip, cheek, and tongue is shown in Table II. Of 128 consecutive determinate cases of cancer of the lip without metastases on admission, in which the primary lesions were controlled for at least five years, only four patients (3 per cent) later developed metastases. In this group, therefore, prophylactic neck dissection could not have had even a theoretic value in 125, or 97.5 per cent, whereas under the higher reported mortality rates following neck dissection, over 10 per cent of the patients would have died of postoperative complications, about four times the number which the procedure could possibly have cured. In any case, even under the lower reported mortality rates, would

it have been worth while to perform 128 neck dissections in order to anticipate metastases in three patients, when as a matter of fact these three were all cured by subsequent treatment? There is a similar trend in cancer of the tongue and of the cheek. If one accepts the proposition that prophylactic neck

TABLE II

HYPOTHETIC LIMIT OF THE VALUE OF PROPHYLACTIC NECK DISSECTION

Prophylactic treatment to the neck could have been of actual value only in those cases admitted without palpable metastases in which the primary lesion was eventually permanently controlled and in which clinically demonstrable metastases appeared at a later date

	Patients Admitted Without Palpable Cervical Metastases in whom the Primary was Permanently Controlled	Patients who Late Developed Cervical Metastases
Cancer of tongue (1931-1934)	40	5 (12%)
Cancer of lip (1928-1932)	128	4 (3%)
Cancer of cheek (1930-1934)	12	2 (17%)

dissection can be of value only when the primary lesions remain cured and when metastases would eventually appear, then only about one in 33 prophylactic neck dissections in cancer of the lip can be of value, one in six in cancer of the cheek, and one in eight in cancer of the tongue.

In the case of radiation, prophylactic treatment as ordinarily given (one to two skin erythema doses to each side of the neck) does not carry with it any mortality, but if it cannot be demonstrated that such radiation is beneficial, then it must be conceded that it is at least wasteful from an economic standpoint even though otherwise harmless. Since such small dosage has never been observed (or at least reported) to sterilize a proven focus of epidermoid carcinoma, why should it be assumed capable of sterilizing an impalpable focus (the actual existence of which cannot be proved) simply because the patient survives and does not subsequently develop metastases?

In the final analysis, it seems to me that the evidence, both theoretic and statistical, fails to provide any justification for prophylactic treatment in intra-oral and pharyngeal cancer. On this basis, treatment is administered only if and when cervical nodes are clinically involved.

Choice of Treatment Methods for Clinically Positive Cervical Metastases—The selection of the particular form of treatment for clinically demonstrable cervical metastases should be based upon the clinical features of the given case rather than on any partisan preference for one or another method. The special indications for radiation and for surgery in cervical metastatic cancer differ widely. It is fortunate for surgery that radioresistance is often associated with the more slowly developing, orderly metastasizing, and less malignant forms of cancer. It is equally fortunate for radiation therapy that the more malignant, rapidly and widely metastasizing lesions not suitable to surgery tend to be among the more radiosensitive. The clinical behavior of a given case of intra-oral or pharyngeal cancer may be predicted with a fair degree of accuracy from the site of the primary lesion and from the histologic type of the growth.

For instance, cancer of the lip is usually squamous carcinoma Grades I or II. The rate of growth is moderate, metastases develop relatively late in the course of the disease, in an orderly manner, and often after permanent control of the primary lesion. For such cases, neck dissection is suitable.

At the other extreme are the highly malignant, rapidly progressing anaplastic growths of the base of the tongue or of the nasopharynx which metastasize early, bilaterally, and widely throughout the neck. While these cases are unsuited to surgery, both because of the location of the primary lesion and because of the histologic character and distribution of the cervical nodes, nevertheless these growths are highly radiosensitive and respond favorably to radiation treatment.

In assaying the relative values of radiation and surgery for cervical metastases, one must admit that each has its own limitations and disadvantages. Little is gained by an attempt to prove the superiority of one method over the other. The two need never be considered as competitive, but rather as complementary, and the selection of the exact treatment procedure in the individual case depends on the experience and ability of the surgeon. An outline of the conditions influencing the selection of treatment methods for cervical metastases is given in Table III.

TABLE III

CONDITIONS INFLUENCING SELECTION OF TREATMENT METHOD IN CERVICAL METASTATIC CANCER

Favorable to Surgery	Metastases Clinically Evident	Favorable to Radiation
(1) Primary controlled		(1) Primary uncontrolled or under treatment
(2) Nodes operable		(2) Nodes inoperable
(3) Metastases unilateral		(3) Metastases bilateral
(4) Radioresistant, histologically differentiated tumors		(4) Radiosensitive, anaplastic tumors
(5) Primary lesions of lip, mucosa of cheek, anterior tongue, floor of mouth or gums		(5) Primary lesions of base of tongue, tonsil, nasopharynx, extrinsic larynx, pharyngeal walls

A combination of radiation and surgery is usually the best solution when an individual case fails to conform in more than one respect to either set of conditions.

Treatment by Radiation—When all primary sites are considered, radiation is undoubtedly more useful—that is, applicable in more cases—than surgery for the treatment of cervical metastases. A combination of protracted fractional x-radiation through narrow skin portals limited to the area immediately adjacent to the node and supplementary implantation of radon gold seeds has proved to be the most efficacious radiation method in the Head and Neck Clinic at the Memorial Hospital. The essential factors in this radiation technique are: First, to deliver a cancer lethal dose to the immediate vicinity of the metastatic nodes with as little damage as possible to the surrounding normal tissues, and, second, to conserve the general tolerance of the patient. The greatest avoidable cause of failure of radiation therapy in any part of the body is the irradiation of unnecessarily large volumes of tissue, so that even though the growth may be destroyed, the patient cannot survive the effects of the treatment.

Aspiration biopsy of at least one involved node should be made in each patient treated by radiation. Such confirmation of the diagnosis is essential for purposes of record. When a node is clinically involved, radiation treatment if otherwise intended should not be withheld or even delayed because of the failure to obtain a positive aspiration biopsy, but the accuracy of the surgeon's clinical diagnosis will be improved if he subjects himself to the discipline of an attempt at histologic confirmation in all cases, and if he limits his claimed cures to those cases which have been so proved.

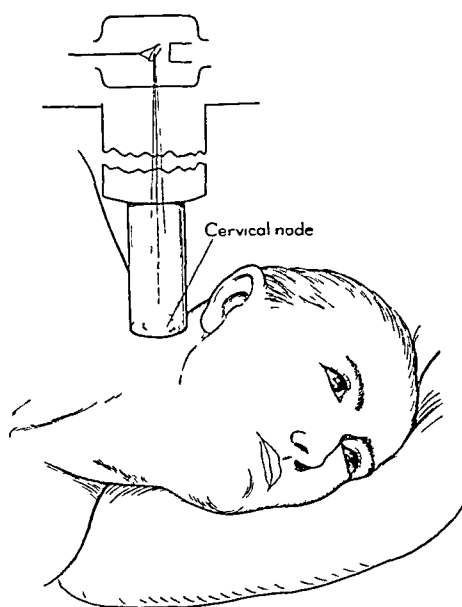


FIG 1—External radiation of a single cervical node. In order to deliver a cancer lethal dose of γ radiation to a single cervical node the beam must be small and directed to the immediate vicinity of the node itself rather than to the entire lymph node bearing area of the neck. Limitation in size and accurate positioning of the skin portal are favored by the use of metal cylinders in direct contact with the skin.

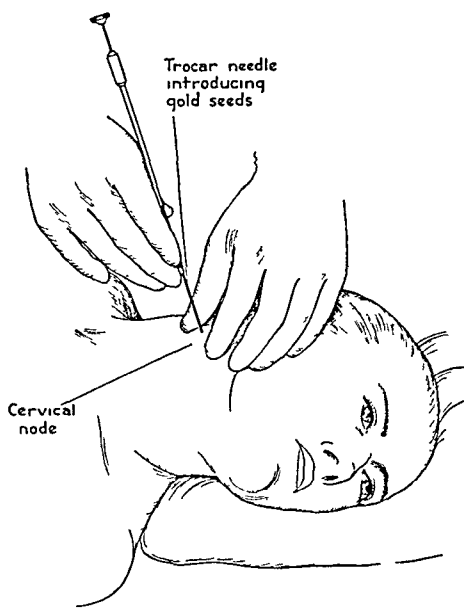


FIG 2—Implantation of radon seeds through the skin. Radon gold seeds may be implanted into a cervical node or into a subcutaneous mass through puncture wounds in the skin—a convenient and time saving method if the node is not situated under too deep a layer of subcutaneous fat.

Fractionated X-Radiation—To localize the external radiation, circular portals are used, limited in size so as to include only the node and a margin of 1–1.5 cm (Fig 1). In the average case, for the treatment of individual nodes such portals will vary between 3 and 5 cm in diameter (the smallest 2.5 cm). Separate portals are used for widely separate nodes. Immediately adjacent nodes are treated as single masses. Depending upon the size of the portal a total of 4,000–8,000 r or even more is given by daily divided doses over a period of two to three weeks. Immediately on the completion of this external dose, radon seeds in a tissue dose of five to ten SED (skin erythema doses) are implanted either through a puncture wound in the skin (Fig 2), or after surgical exposure of the outer surface of the node.

Surgical exposure is indicated when the node lies deeply under a thick layer of subcutaneous fat, where the accurate placement through skin punc-

tures is not possible by palpation alone. In these cases, it is advisable to anticipate the radiation skin reaction by performing the surgical exposure at the end of about two weeks of x-radiation.

Such a plan of localized irradiation of individual nodes, based upon the principle of treating cancer only when and where it is at least clinically present, makes it possible to treat several separate involved nodes in the same case. One of the difficulties in the way of the general acceptance of this plan of treatment by surgeons is that it contravenes an accepted principle which is entirely reasonable when applied to surgery alone, namely, that in neck dissection the entire mass of lymph node bearing tissues of one side of the neck should be removed. In radiation therapy the opposite holds true—radiation of the entire neck in cancer lethal doses is dangerous, and far better results will be obtained by local and individual treatment of each separate involved node.

Interstitial Radiation—When radium emanation is available, there can be little question but that radon gold seeds are the most useful form of interstitial applicator for supplementing fractionated x-radiation. In the small nodes, the supplementary seeds in a single tissue dose of five to six S E D are implanted after about two to three weeks of fractionated x-radiation. In the larger more resistant masses the dose of radon seeds is also fractionated, and the series of external treatments is interrupted at about seven- to ten-day intervals, and two or even three fractions of radon seeds are given. In the more difficult cases the total doses of both x-radiation and seeds should approach the local and general tolerance. The dosage in such cases is empiric and so variable as to be learned only by experience. Radon seeds alone are sometimes satisfactory for small or moderate-sized nodes up to 1.5 cm in diameter.

Treatment by Surgery—The only justifiable surgical method for the treatment of cervical metastases is neck dissection, which implies the complete removal in a given area of all lymph-node-bearing tissues between the superficial subcutaneous fat and the fascia covering the deep muscles of the neck. The extent of such an operation may vary from a local dissection of the submental and submaxillary triangles to a complete or block dissection extending from the lower edge of the mandible and the mastoid to the clavicle, and from the anterior border of the trapezius forward to the midline. A form of incision, usually a variation of the crucial or the trifurcate, should be selected which will permit adequate exposure of the operative field. Details of block neck dissection as performed in the clinic at the Memorial Hospital are given in Figures 3-6, inclusive.

Local is preferable to general anesthesia. The highest mortality rates are usually reported from those clinics where general anesthesia is used routinely. At the Memorial Hospital, in 210 neck dissections performed on the Head and Neck Service over a ten-year period from 1930-1939, inclusive, there were five postoperative deaths, a mortality of 2.4 per cent in the whole group (Table IV). In 196 operations performed under local anesthesia, there were only three deaths, a mortality of only 1.5 per cent. Two of the deaths occurred

in the 14 operations performed under general anesthesia, a mortality of 14.3 per cent. In extenuation of the higher mortality in the latter group, it should be stated that general anesthesia was used only for the most difficult and complicated situations where the nature of the procedure would have rendered

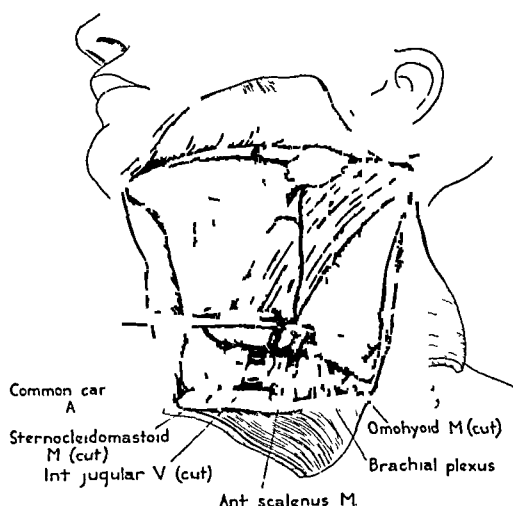


FIG 3—A form of incision is selected (trifurcate, crucial, or a modification) which will permit of adequate exposure of the operative area. The skin flaps are dissected back. A complete or block dissection begins at the clavicle where the sternomastoid muscle, the internal jugular vein and the omohyoid muscle are cut across.

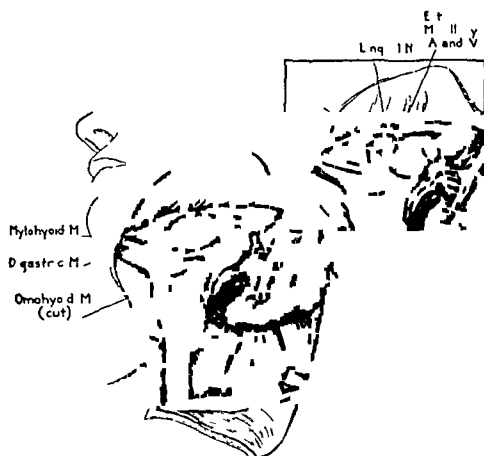


FIG 4—The limits of a complete unilateral block dissection are the midline anteriorly, the border of the trapezius muscle posteriorly, the clavicle below, and the submental space and the lower border of the mandible superiorly. The deep level of the dissection is the fascia overlying the pretracheal and lateral cervical muscles. The common carotid artery, the vagus and the phrenic nerves, and the origin of the brachial plexus are exposed. The submaxillary salivary gland and the contents of the submaxillary triangle are removed down to the level of the mylohyoid and hyoglossus muscles. The sensory branches of the cervical plexus are excised. The accessory nerve is sacrificed.

local anesthesia inadequate. At the present time, it is rarely necessary to employ the more dangerous general anesthesia for this operation.

TABLE IV
NECK DISSECTIONS FOR CERVICAL METASTATIC CANCER
January 1, 1930 to December 31, 1939

Total Neck Dissections		210
Local anesthesia		196
Postoperative deaths		3
Postoperative mortality	1.5%	
General anesthesia		14
Postoperative deaths		2
Postoperative mortality	14.3%	
Total postoperative mortality	5 cases	2.4%

Treatment by Combinations of Radiation and Surgery—The value of preoperative and postoperative radiation in small doses is often brought up for discussion. Until about 1930 it was a common practice in all cancer clinics to apply small doses (one to two S.E.D.) of radiation to the operative field either immediately before or immediately after practically all operations for cancer (neck, breast, pelvis, extremities, etc.). The theory for giving preoperative radiation was that the malignancy of the tumor and its tendency

toward dissemination during the operation would thereby be reduced. The theory for giving postoperative radiation was that if any cancer cells had been missed or had been spilled into the operative wound, these small doses of radiation would destroy them so that subsequent recurrence would not take place. From what is now known of cancer-lethal radiation dosage, one



FIG 5—In order to remove the submaxillary salivary gland, the submaxillary duct and the facial vessels are cut and ligated.

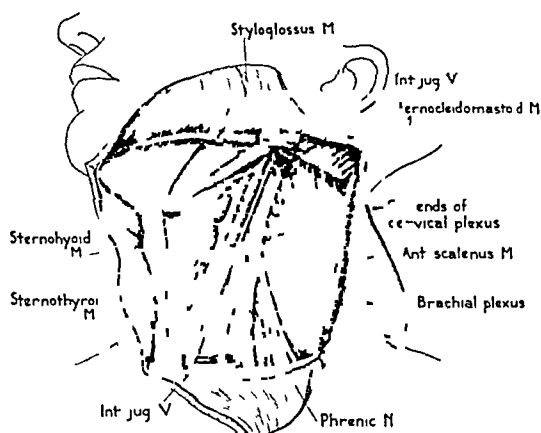


FIG 6—The dissection is completed by cutting across the tip of the parotid gland and across the upper portion of the sternomastoid muscle. Great care is taken to remove completely the subdiaphragmatic lymph nodes which lie just below and under the inferior edge of the posterior belly of the digastric. At this point, the internal jugular vein is ligated and cut across.

to two SED will not sterilize epidermoid or adenocarcinoma, and in my opinion there is no sound evidence that it can produce even a deterrent effect which will in any way modify the pre- or postoperative course. The attempts to apply cancer lethal doses pre- or postoperatively usually result in rather tragic failures of wound healing.

I mention such pre- and postoperative radiation measures only to point out that I do not include them under the definitely worth while and effective combinations of radiation and surgery which will be discussed in the following paragraphs.

Combinations of Surgery and Heavy Radiation—The conditions under which effective combinations of surgery and radiation are useful can best be illustrated by citing examples. Metastatic nodes from cancer of the tongue, cheek, or lip are sometimes infected and centrally necrotic with perforation of the node capsule and invasion of the adjacent tissues. With surgery alone, the possibility of complete removal of such nodes is rather remote. With radiation alone, a lethal dose to the entire volume of the necrotic node will invariably bring on a further breakdown of the tissues and a discharging sinus which is slow to heal. Such patients may often be successfully treated by applying a dose of radiation (radon seeds alone or combined with external radiation),

following which the height of the radiation reaction is anticipated by surgically excising the condemned mass of tissue

The two methods may also be effectively combined during neck dissection when a metastatic node, thought to be operable, is found to infiltrate beyond its capsule into a structure which cannot be widely excised. In such a case, a small remnant of the tumor, 1–1.5 cm in diameter, may be left and a heavy dose of radon seeds inserted immediately, the remainder of the neck dissection proceeding as usual. At the Memorial Hospital, it is a routine practice to have radon gold seeds available for such a contingency in all neck dissections.

Prognosis—The prognosis in cervical metastatic cancer is by no means hopeless, despite the rather discouraging opinions sometimes expressed by both surgeons and radiologists. The chance of cure is best in those patients who develop metastases late in the course of the disease, especially after control of the primary lesion (Table V). It is worst in those who already have metastases at the time of their first examination. The chance of cure in the bilaterally metastasizing, highly anaplastic tumors, such as cancer of the nasopharynx, hopeless heretofore by surgical treatment alone, has been so much improved by the advent of modern radiation therapy as to approach the results by surgery in the highly differentiated radioresistant and slowly metastasizing tumors such as cancer of the lip. The cure rates shown in Table V are calculated on consecutive cases of patients in all stages of the disease treated by radiation or surgery or combinations of the two. From these statistics, it is apparent that the capacity to metastasize and the presence of metastases at some time during the course of the disease are the most significant factors in the prognosis of any form of cancer.

TABLE V
THE INFLUENCE OF METASTASES ON THE PROGNOSIS
OF INTRA-ORAL AND PHARYNGEAL CANCER

Site of Primary Growth	Total No of Cases	Five-Year Cure Rate		
		With Metastases %	Without Metastases %	All Cases Percentage
Lip	313	27	95	70
Cheek	78	21	30	27
Tongue	208	12	45	25
Floor of mouth	87	22	29	25
Gingiva	85	8	42	24
Palate	57	6	54	21
Tonsil	148	10	38	18
Nasopharynx	80	20	47	25

ILLUSTRATIVE CASE REPORTS OF CERVICAL METASTASES FROM INTRA-ORAL CANCER

Case 1—Cancer of the Tongue. J. A., male, age 67, admitted November, 1932, complaining of sore on tongue of two months' duration, which had gradually increased in size. The patient gave a history of having been a heavy cigar smoker until six months before admission. The Wassermann was negative. The lesion, 2 cm in diameter, raised and partly ulcerated, was located on the left side of the dorsum of the tongue, 2.5 cm

back from the tip The biopsy showed squamous carcinoma Grade II There was no palpable adenopathy

After implantation of 15 mc of radon gold seeds, the lesion regressed and the patient remained well until March, 1933, when an enlarged node, 2.5 cm in diameter, appeared over the left upper, deep cervical region An aspiration biopsy was positive for metastatic cancer In April, 1933, the outer surface of the node was surgically exposed, and 27 mc of radon gold seeds were implanted After healing, a scarred, indurated mass remained in this region, but the patient has been otherwise free of disease for seven years

Case 2—Cancer of the Floor of the Mouth J C, male, age 67, admitted November, 1932, complaining of soreness in the floor of the mouth of one year's duration He had been treated by his family physician with repeated applications of silver nitrate Three weeks before admission, following severe pain, the patient examined his mouth and found an ulcer He gave a history of having smoked a pipe excessively for years The Wassermann was negative The lesion was located in the midline of the floor of the mouth, partly ulcerated, indurated, 2 cm in diameter and infiltrating to a depth of about 1 cm The biopsy showed squamous carcinoma Grade II There was no cervical adenopathy

Treatment was given by roentgenotherapy through portals, 5 cm in diameter, one directed to the submental region and one to each side of the chin, for a total dose of 2,400 r \times 3 There was apparent complete regression, but residual disease was proved by biopsy three months later, and 8 mc in radon gold seeds were implanted This treatment was followed by localized radium necrosis which did not heal entirely for one year

In July, 1933, enlarged nodes appeared over both submaxillary regions, overlying the submaxillary salivary glands Aspiration biopsy of the node on the right was diagnosed as metastatic cancer Radon seeds were implanted in both submaxillary nodes through the skin, 26 mc on the left and 10 mc on the right The patient remained well until October, 1935, when a biopsy from a suspicious area in the floor of the mouth was positive The recurrence was treated by actual cautery in November and again in December, 1935 Since that time the patient has remained free of disease—in the neck since 1933, and in the floor of the mouth since 1935

Case 3—Cancer of the Tongue H R, male, age 58, admitted in June, 1936, with an ulcer on the tongue of two months' duration, accompanied by some pain The patient gave a history of white spots on the lips and tongue for 25–30 years, and stated that he smoked five to six cigars daily The Wassermann was positive The lesion, centered 4 cm back from the tip of the tongue, was 3 cm in diameter, infiltrating to a depth of 1 cm The biopsy showed squamous carcinoma Grade II There were no palpably enlarged lymph nodes

The lesion was treated with peroral x-radiation (3,500 r, cone 4 cm, T S D 65 cm) and 8 mc of radon gold seeds In September, 1936, an enlarged node appeared over the right submaxillary salivary gland An aspiration biopsy showed squamous carcinoma The node was treated with 5,500 r through a 4 cm portal It became fluctuant and was obviously liquefying In October, 1936, a neck dissection was performed The node was found to be an abscess about 4 cm in diameter on the mesial aspect, infiltrating the mylohyoid and hyoglossus muscles, the latter area was not considered surgically removable since it extended into the tongue Twenty-six millicuries of radon gold seeds were implanted into the residuum which could not be removed, and the neck dissection proceeded as usual The patient has remained well for three and one-half years A lesion on the lip which was a papilloma and leukoplakia only was treated by radiation and regressed completely

End-Results—It is difficult to gather any very definite data from the medical literature concerning the actual cure rate in cervical metastatic cancer A few pessimistic surgeons and radiologists report that they have never ob-

tained cures once intra-oral or pharyngeal cancer has spread to the neck. Most investigators, however, report cures, but the statistics, for the most part, are based upon series of neck dissections for lip cancer only and have, therefore, only a limited significance in regard to the whole problem, since cancer of the lip is the most easily cured of all forms of intra-oral cancer, both at the primary site and in the cervical nodes. Some of these authors have not separated the cases with histologically positive nodes from those with negative nodes, and the actual cure rate for metastatic cancer is, therefore, obscured.

TABLE VI

NECK DISSECTIONS FOR CANCER—JANUARY 1, 1930 TO APRIL 1, 1934

Successful Results in Cases with Histologically Positive Nodes

	Total No of Cases	Five Year Survivals	Lost Without Recurrence
Cancer of lip	21	5	2
Cancer of tongue	18	2	0
Cancer of floor of mouth	5	3	0
Cancer of buccal mucosa	6	3	1
Cancer of tonsil	4	1	1
Cancer of salivary gland	2	1	1
Cancer of cervical lymph nodes (primary undetermined)	1	0	0
Cancer of skin of head and neck (including melanoma of skin and orbit)	8	0	0
Cancer of lung	1	0	0
Cancer of extrinsic larynx	1	0	0
Lymphosarcoma of neck	1	1	0
Hodgkin's granuloma	2	1	0
	70	17	5
Total number of cases			70
Lost without recurrence			5
Total determinate group			65
Five year survivals			17
Net cure rate (17/65)			26%

Using only proven nodes, end-results could be calculated in more than one way. The efficacy of neck dissection in selected, early, operable cases, all histologically positive (Table VI) is proved by the fact that 26 per cent have survived for over five years. Since all cervical nodes not treated by surgery, including the inoperable and hopelessly advanced and palliative cases, receive radiation, no cure rate percentage can be calculated for any significant comparison with neck dissection. It has been stated, however, by some authors that there is no authentic case of a five-year cure of proven cervical metastases treated by radiation alone. In answer to such statements, I wish to place on record the data given in Table VII. At the Memorial Hospital, 46 patients with histologically proven metastatic cancer treated by radiation alone survived for five years or more. These cases do not necessarily represent all the cures, but only those in which aspiration biopsies were made. To-day aspiration biopsy is part of the routine in all cases, it will be noted that the numbers of proven successes have increased in the later years.

CERVICAL METASTATIC CANCER

TABLE VII

HISTOLOGICALLY PROVED CASES OF CERVICAL METASTATIC CANCER
TREATED BY RADIATION ALONE

Free of Disease March 1, 1939

Five Years or More		Less than Five Years	
Prior to 1930	4	1935	12
1930	5	1936	13
1931	5	1937	19
1932	12		
1933	10		
1934	10		
Total	46	Total	44

DISCUSSION —DR WILLIAM F MACFEE (New York) Doctor Martin's approach to the study of cervical node metastases is somewhat different from that to which some of us are accustomed. Ordinarily, one thinks of the various primary lesions as producing certain percentages of metastases, whereas Doctor Martin presents the percentages of cervical metastases which have been produced by the various primary lesions. Cancer of the floor of the mouth, for example, presents an incidence of cervical metastasis amounting to something like 30 or 40 per cent, if the cases are taken in series as they enter the hospital. As seen from the reverse point of view, 9 per cent of cervical node metastases are produced by cancer of the floor of the mouth.

When one attempts to determine clinically whether the cervical nodes are involved in a particular case he is confronted with a considerable chance of inaccuracy. When the nodes erroneously considered involved are added to those erroneously thought not to be involved, the total error is about 40 per cent.

The simplest solution of the problem of node invasion is either to consider all nodes involved and treat them accordingly, or to regard them as uninvolved until proven to be involved. The first point of view will, undoubtedly, lead to many unnecessary node dissections, as Doctor Martin has indicated, but the opposite point of view will, just as certainly, lead to delay in the treatment of many cases with involved nodes. It may be reasonably questioned whether the uncompromising adoption of either attitude is to the best interests of the patient.

One of the difficulties in statistical presentations on the subject of cancer is the notable lack of uniformity in the selection of cases, one series is often not truly comparable to another. A real advance will be made when statistics on cancer of any part of the body, the tongue or breast, for example, are based upon all the cases observed in a particular clinic over a definite period of time. Subgroupings could then be considered in relation to the whole experience.

It is very encouraging to see that so many patients with cervical node metastases treated by radiation alone have survived the five-year period. Many physicians have acquired the belief that cancer in lymph nodes cannot be destroyed by radiation and it is gratifying to be shown that such is not the case. It cannot be doubted that radiation has a definite usefulness in the treatment of cervical node metastasis, particularly in the group of undifferentiated tumors which occur so frequently in the region of the tonsil and pharynx.

DR JOHN M HANFORD (New York) Doctor Hanford said that ten years ago a Head and Neck Neoplasm Clinic had been started at the Vanderbilt Clinic and the Presbyterian Hospital with Dr A P Stout, the pathologist, Dr Maurice Lenz, the radiotherapeutist, and himself, as surgeon. During

those ten years, Doctor Hanford said, he had become very much impressed with the value of radiation therapy

To-night certain things were brought out Doctor Martin did not mention external irradiation by radium, but roentgenotherapy alone apparently cannot be counted upon to cure squamous cell metastatic carcinoma in the cervical lymph nodes Interstitial treatment by radon, however, has been demonstrated to bring about five-year cures in certain cases These are real contributions

There is a great difference between the anterior part of the tongue and the posterior part, as there is, also, between the lip and the tongue In carcinoma of the posterior part of the tongue, radical neck dissection is rarely indicated Carcinoma of the anterior two-thirds of the tongue is much more likely to need radical neck dissection, even though no nodes are palpable Carcinoma of the lip rarely needs treatment of the neck

Another phase of this subject mentioned by Doctor Hanford was the fact that occult metastases may be present when no nodes are palpable, or when nodes are slightly palpable One must assume, for example, that in carcinoma of the tongue, there is a high percentage of cervical metastases Should one await the appearance of a node sufficiently large to be identified as feasible to treat with interstitial radon? This delay and this treatment of only such palpable disease court disaster for the patient This sort of treatment is a makeshift, and while valuable in certain patients, such as those unsuited to withstand a radical neck dissection, it is not the ideal or the standard method of protecting the patient who has carcinoma of the anterior part of the tongue The ideal is radical neck dissection, preferably before and certainly after nodes become suspected The very presence of a node sufficiently large to treat with radon presupposes, even more, the presence of occult metastases Therefore, the treatment by radon, interstitially, of this palpable metastatic disease must be admitted as incomplete

The same principles hold in carcinoma of the lower lip, but because cervical metastases from the lip are less common than from the tongue, the indications for treating the neck in lip carcinoma are less compelling

Doctor Hanford also referred to nodes which are large, firm, extensive or adherent, and recalled that three years ago he presented before the N Y Surgical Society a series of patients representing an advanced stage of cervical metastases treated by radical neck dissection There were more than 7 per cent five-year cures in a few such patients, which means that this "stage three" of Lacassagne is not necessarily hopeless These patients were treated mainly by surgery Some had roentgen or radium therapy, but without the surgery any good radiotherapist would have admitted they could not have been cured Surgery, therefore, may play a part in very extensive disease Even though adherent to the muscle or vein, it is still possible that radical surgery may cure the patient

Finally, Doctor Hanford felt that the average surgeon using rectal ether anesthesia, in a long neck dissection, with careful hemostasis, gentle manipulation, and with true cancer surgery, is going to do better work than with local or regional anesthesia

DR HAYES MARTIN in closing, said that both Doctor MacFee and Doctor Hanford have called attention to the fact that it is sometimes difficult to diagnose metastatic nodes by palpation Doctor Martin admitted this difficulty, but said he believed that the surgeon's accuracy of clinical diagnosis will steadily improve if he makes a definite preoperative diagnosis in each case, records this diagnosis in writing on the chart, and checks it with the postoperative histologic examination Aspiration biopsy is useful in doubtful cases, especially where neck dissection would be attended by considerable risk

because of the patient's general condition. In any case, the surgeon should hold himself responsible for the accuracy of his preoperative clinical diagnosis and should consider it a reproach to find too many of his neck dissections negative on histologic examination.

In the diagnosis of metastatic cervical cancer, it is not particularly illuminating to state that the lymph nodes are "not palpable" in a given case. He stated that in his experience, normal lymph nodes are palpable in practically all healthy subjects. The problem is to decide whether or not the palpable nodes have been invaded by cancer.

✓ The question as to whether prophylactic neck dissection is justifiable in the treatment of cancer should, and he said that it seemed to him to be settled only after an analysis of the clinical behavior of large series treated, on the one hand, and by prophylactic neck dissection and, on the other, by a "watchful waiting" policy. Prophylactic neck dissection could benefit only those patients who are admitted without nodes and later develop them. According to such analyses prophylactic neck dissection can be of value in only one case in eight (12 per cent) in cancer of the tongue, and in only one case in 33 (3 per cent) in cancer of the lip. It seemed to him that this percentage was too small to justify routine dissection, especially when the procedure is accompanied by a definite mortality. Under the higher mortality rates for neck dissection (10 per cent), this procedure would kill as many as it could possibly cure—and in some cases more. In any event, it is too serious and costly an operation to be undertaken when the percentage of patients benefited is so small.

DOCTOR MARTIN stated that since, from a consideration of his own and other published figures it is obvious that general anesthesia almost quadruples the operative mortality in neck dissection, he failed to see how Doctor Hanford could reasonably maintain his advocacy of rectal ether for this procedure.

Read before the New York Surgical Society, April 24, 1940

PSEUDOGASTRITIS OF OPERATIVE ORIGIN

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PEPTIC ULCER is believed by many clinicians always to be associated with gastritis, and the latter has been thought to be an important etiologic factor in the production, maintenance, and recurrence of peptic ulcerations. One of the chief arguments in favor of this concept comes from the study of resected surgical specimens.

Recently, Schindler,¹ and his coworkers, have suggested that some of the pathologic changes which have been observed following resection of the stomach were artefacts produced during the gastrectomy. In a series of experiments upon normal dogs these workers were able to reproduce typical gastric changes in devascularized segments of the stomach which contained free hydrochloric acid. They believed that the changes which they observed were produced by the action of the hydrochloric acid on gastric mucosa which had become devitalized during operation. Some years previously, Afendulis and Gulzow² reported that following portal venous obstruction in dogs the gastric changes commonly associated with gastritis were observed. They postulated that the gastritis was caused by a circulating toxin, liberated from the damaged liver itself, or from the markedly congested gastro-intestinal tract.

Clinics in this country and abroad have reported^{3, 4, 5} a wide variation in the incidence of gastritis in surgical specimens. This can hardly be explained by variations in the concentration of free hydrochloric acid in the stomach. However, individualities in surgical technic permit wide fluctuations in the degree of engorgement encountered in the stomach during the performance of a partial gastrectomy. It seemed important to study whether or not this factor might not be the significant variable accounting for the varying degrees of gastritis observed in surgical specimens.

Methods—Healthy dogs, weighing between 5.4 and 17.6 Kg., were selected for the experiments. They were fasted for 24 hours before beginning the experiment. Gastric lavage was routinely performed in the first few experiments but so little material was recovered that it was discontinued thereafter. The animals were anesthetized with sodium amytal administered intraperitoneally.

As is well known, the stomachs of fasting dogs commonly contain no free hydrochloric acid. In the experiments in which it was desired to assure the presence of this acid, it was often induced by the administration of one milligram each of histamine hydrochloride and acetyl-beta-methylcholine chloride given

one-half, one, and one and one-half hours before beginning the operation. In other instances 0.1 N hydrochloric acid in amounts varying from 40 to 80 cc was injected directly into the stomach cavity by syringe and needle after celiotomy. No difference in the end-results could be distinguished in the results from these two modes of producing an adequate supply of free hydrochloric acid.

In order to eliminate other factors as responsible for the production of gastritis in these studies a series of control experiments was undertaken.

In one dog, following a midline abdominal incision, the stomach was excised *in toto*, rapidly, without the use of intestinal clamps, and without ligating or applying hemostats to the vessels. No free hydrochloric acid was induced, and a negative reaction to Topfer's reagent was obtained from the gastric secretions. The resected segment was placed in a specimen pan for two hours. Biopsies were then taken from various portions of the stomach. These provided sections which we used for later comparison.

Control Experiments—(1) This group consisted of two animals. The presence of free hydrochloric acid was induced as discussed above. The abdomen was opened by a midline abdominal incision and a soft rubber-covered clamp was loosely applied to the duodenum to prevent the copious acid-containing secretions from passing down the intestinal tract. At the end of two hours, the stomach was excised *in toto*, biopsies were taken from various areas, and the specimens preserved. No significant gross or microscopic changes were found.

(2) This group consisted of five animals. No free acid was induced and none was found present. After a midline incision through the abdominal wall, the pylorus was delivered into the wound and the duodenum was severed between intestinal clamps. An intestinal clamp was applied across the midportion of the stomach, in two instances a rubber-covered clamp, and in three instances a crushing clamp of the Payr type was used. The distal half of the stomach was freed of its vascular attachments. This was done rapidly in order to prevent any unligated artery from continuing to pump blood into the isolated segment and thus produce engorgement. The intestinal clamps were applied for two hours, after which time the stomach was excised *in toto*. Biopsies were taken from various areas of the resected segment. No important gross or microscopic changes were found.

(3) This group consisted of six animals. No free hydrochloric acid was present. It was similar to Group 2, except that in these dogs engorgement of the segment was encouraged. This was accomplished by slowly ligating the vessels and allowing the left gastric artery to pump blood into the otherwise isolated segment for approximately ten minutes before this artery was also ligated. The specimens were left *in situ* and at the end of two hours the entire stomach was excised. Biopsies were then taken. The changes observed were proportional to the degree of engorgement which had taken place (Fig. 1). In the main these consisted of cyanosis and edema of the mucosa. In one instance, in which the left gastric artery was allowed to

pump blood into the otherwise completely devascularized stomach, severe hemorrhages were observed in all coats of the gastric wall. There was massive edema and cyanosis, but the surface epithelium was everywhere intact (Fig 2)

Experimental Procedures—Following the completion of the control series, two groups of experiments were undertaken. In both groups the presence of free hydrochloric acid in the stomach was assured by the methods previously described. An attempt was made in both groups to duplicate the



FIG 1—Vascular congestion—no hydrochloric acid. Duration two hours ($\times 230$). Note the intact mucosal epithelium and the engorgement of the mucosal capillaries.



FIG 2—Massive congestion—no hydrochloric acid. Duration three hours ($\times 150$). There is extensive mucosal hemorrhage, with compression and disruption of the glandular crypts. The surface epithelium shows no erosion or necrosis.

conditions encountered in the performance of a partial gastrectomy in a surgical clinic.

(A) This group consisted of 23 animals. After a midline abdominal incision, the duodenum was severed between intestinal clamps. The circulation to the distal half of the stomach was rapidly occluded by the simultaneous closure of clamps previously placed across the midportion of the stomach and on the vascular attachments of its greater and lesser curvatures. This technic was designed to prevent vascular engorgement of the distal portion of the stomach. In most instances the resection was not completed but the abdomen was closed over the clamps. At the end of periods varying from 60 to 180 minutes, the incisions were reopened, and, as a rule, the stomach excised *in toto*. In a few instances the completely devascularized segment was immediately resected and then placed in a specimen dish with the clamps and ligatures *in situ*. These specimens were examined after similar periods of time had elapsed and biopsies were taken.

(B) This group consisted of 18 animals and was in all respects similar to the preceding group, except that an attempt was made to encourage engorgement in the portion of the stomach proposed for resection. This was accomplished by placing an intestinal clamp across the midportion of the stomach in such manner as not to occlude the left gastric artery. The duodenum was severed between intestinal clamps. With the exception of the left gastric artery the vascular connections along the greater and lesser curvature of the portion of the stomach proposed for resection were then ligated and divided. The left gastric artery was isolated and was allowed to pump blood for ten minutes into the segment of stomach having no vascular out-flow. The stomach was either left *in situ* or, in a few instances, immediately excised with the clamps remaining in place on the resected segment. The specimens were examined in from 30 to 180 minutes after beginning the resection.

In two animals in this group the stomach was filled with 0.1 N hydrochloric acid and rubber-covered clamps placed across the midgastric area. The arterial ligations were done so that in one dog marked engorgement was produced in the upper half of the stomach while in the other dog only the lower half was allowed to become engorged. The specimens were both examined at the end of two hours.

Biopsies were then taken and the specimens preserved.

TABLE I

RESULTS OF EXPERIMENTS IN WHICH VASCULAR ENGORGEMENT OF THE DISTAL PORTION OF THE STOMACH WAS AVOIDED DURING THE PERFORMANCE OF A PARTIAL GASTRECTOMY

Dog No	Engorgement		Free HCl	Time in Minutes	Gastritis	
	Gross	Micro			Gross	Micro
20	0	0	+	60	0	0
103	0	+	+	65	0	0
101	0	+	+	75	0	0
102	0	+	+	90	0	0
104	0	+	+	90	0	+
17	0	0	+	120	0	+
18	0	0	+	120	0	0
562	+		+	120	+	
108	0	0	+	120	0	+
109	0	0	+	120	0	+
205	+		+	120	+	
202	+	+	+	120	+	++
304	±		+	120	+	
208	0		+	120	0	
201	+	0	+	132	0	0
106	0	0	+	135	0	+
105	0	+	+	142	0	+
408	+	+	+	180	0	0
303	0		+	180	0	
301	0		+	210	0	

Results—In Table I are charted the results obtained in those experiments in which vascular engorgement was avoided as far as possible. There is a notable absence of gastritis regardless of the time factor and of the presence of free hydrochloric acid (Fig. 3). Minor degrees of gastritis when present were usually associated with slight engorgement which resulted despite our



FIG 3—No congestion—free hydrochloric acid present Duration two hours
($\times 150$) The mucosal epithelium is everywhere intact

TABLE II

RESULTS OF EXPERIMENTS IN WHICH VASCULAR ENGORGEMENT OF THE DISTAL PORTION OF THE STOMACH WAS ENCOURAGED DURING THE PERFORMANCE OF A PARTIAL GASTRECTOMY

Dog No	Engorgement		Free HCl	Time in Minutes	Gastritis	
	Gross	Micro			Gross	Micro
19	++	+++	+	30	+	0
21	++	++	+	30	+	+
22	++	++	+	45	+	0
14	+++	+++	+	60	+++	+++
5	++	+	+	75	+	+
6	++	+++	+	120	+	++
12	+	+	+	120	+	+
107	++	+++	+	120	+++	+++
206	+	++	+	120	++	0
13	++++	++++	+	120	++++	++++
8	+++	+++	+	120	++++	+++
15	+++	++++	+	120	++++	++++
16	++++	++++	+	120	++++	++++
204	+	+	+	125	+	+
209	++	++++	+	125	++	+++
310	++	++	+	150	+	++
305	++++	++++	+	150	++++	++++
307	+++	+++	+	150	+++	+++
409	+++	++	+	180	++	+
308	++	++++	+	180	++	+++
309	++	++++	+	180	+++	+++

attempts to prevent it. In the majority of these specimens a tenacious white film of exudate covered the mucosal surface but no other changes were noted. This film was found to consist of coagulated mucin (Fig 4)



FIG 4—No congestion—free hydrochloric acid present. Duration two hours ($\times 150$). Note the absence of vascular congestion and the amorphous exudate on the surface of the undamaged epithelium.

In Table II are given the results obtained in those experiments in which vascular engorgement was encouraged in the presence of free hydrochloric acid. The high incidence of gastritis in this group was proportional to the degree of engorgement. Gastritis was slight or absent in those experiments in which the time interval from beginning the resection to examination of the specimen was less than 60 minutes. In the process of devascularization of the entire stomach of two animals in this group, marked engorgement was produced in the upper half of the stomach in one, while in the other, only the lower half was allowed to become engorged. At the end of two hours only the engorged segments showed evidences of gastritis.

Gross Pathology—The typical gross pathologic features of the gastritis

observed in these experiments consisted of varying degrees of mucosal edema and cyanosis, petechial and major hemorrhages on the mucosal surface, and superficial erosions. In all cases an exudate covered the mucosal surface. This exudate, composed of coagulated mucin and cellular debris (Fig 5), and stained with acid hematin varied in appearance and consistency, but was usually mottled greenish- or brownish-white in color. The fluid contents of the isolated segments were streaked with a small collection of brownish acid hematin.



FIG 5.—Vascular congestion—plus hydrochloric acid. Duration one hour ($\times 150$). There is erosion of the mucosa. The exudate is composed of cellular debris and erythrocytes.

Histopathology—The characteristic microscopic findings consisted of varying degrees of erosion, mucosal and submucosal engorgement, and edema. We did not observe the leukocytic infiltration of the mucous membrane described by Schindler,¹ and others^{5, 6}. In many instances eroded mucosal capillaries could be seen, in the lumina of which hemoglobin had been changed to acid hematin by the action of hydrochloric acid (Fig 6).

Discussion—The destructive action of the hydrochloric acid of gastric juice upon devitalized tissue has long been recognized. The work of Mor-

ton,⁷ and Dragstedt⁸ has demonstrated the importance of the blood supply in preventing digestion of portions of liver, spleen, and kidney transplanted into the gastric wall. Schindler's experiments suggest that anemia is the devitalizing factor responsible for the striking changes produced by the action of hydrochloric acid on the devascularized gastric segment.

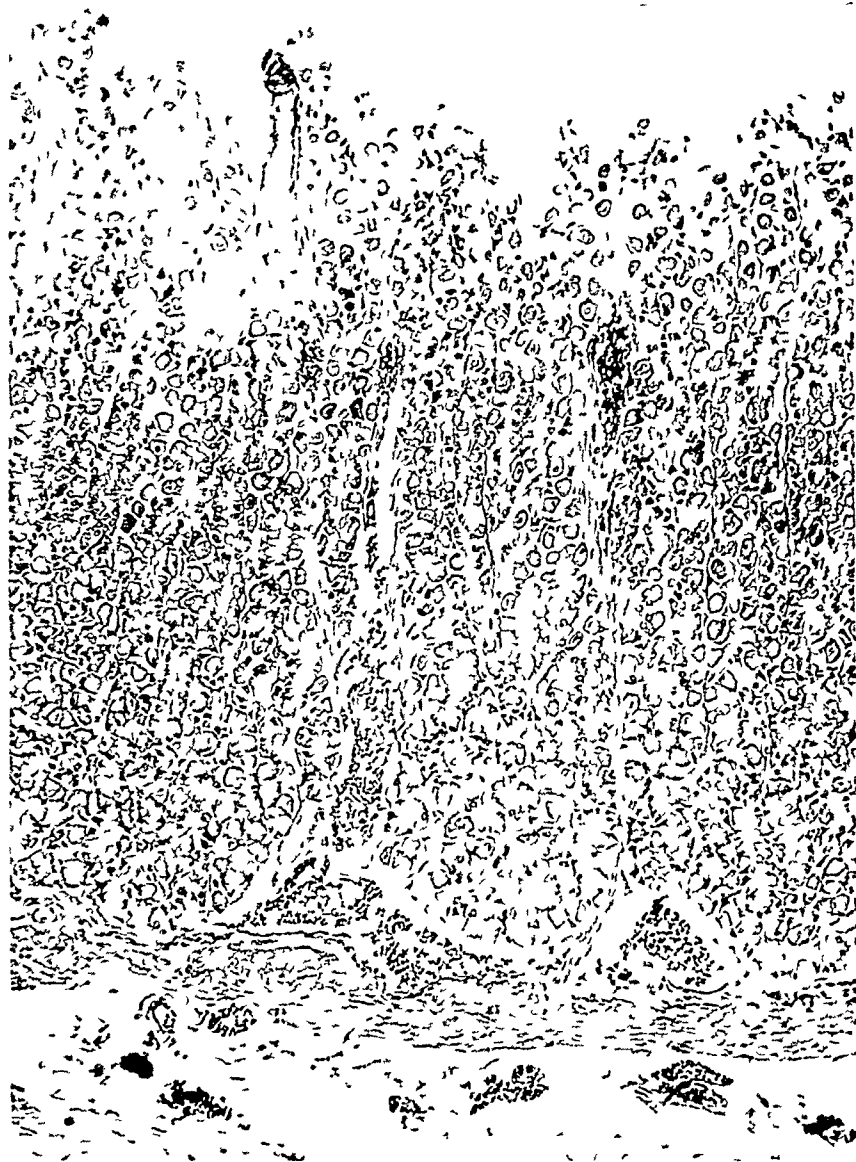


FIG. 6—Vascular congestion—plus hydrochloric acid. Duration two hours (X150). There is marked erosion and superficial destruction of the mucosal epithelium. Three mucosal capillaries are shown to have been tapped by the erosive process. The stained section demonstrates that the hemoglobin of the erythrocytes contained in these vessels has been changed to acid hematin.

Afendulis and Gulzow² were able to produce similar changes in living animals following experimental stenosis of the portal vein. Their animals survived for periods of from four to six weeks, and well-defined gastritis was present as early as five to eight days postoperatively. Changes were most marked in the fundus and corpus, while the antrum was relatively unaffected. The animals were periodically gastroscoped throughout their postoperative course and, in several instances, subsidence of gastritis was

found at autopsy to coincide with the development of an efficient collateral circulation. Severe chronic passive congestion of the abdominal viscera was present in all animals showing gastritis. Foci of necrosis were seen in the liver in many animals. Afendulis and Gulzow suggested that toxic split-products of protein which attacked viscera already devitalized by the asphyxia of congestion, were liberated either from the damaged liver or from the chronically congested gastro-intestinal tract. They supported this contention by supposedly demonstrating an abnormally high histamine level not only in the portal but in the systemic venous blood of their animals. Periodic gastric analyses showed hypersecretion of acid. Konjetzny⁹ also endorsed the theory that engorgement predisposed to gastritis by lowering the vitality of the gastric mucosa. He too recognized the necessity for a second, toxic factor, but was unable to specify its nature.

Our findings and those of Schindler and his associates strongly suggest that the toxic agent postulated by Konjetzny, and by Afendulis and Gulzow, is hydrochloric acid and that asphyxia is the devitalizing factor which renders the gastric mucosa vulnerable to the action of this agent. The present experiments demonstrate that while erosion of the mucous membrane may occur in the presence of hydrochloric acid, in the nonengorged devascularized stomach it proceeds much more rapidly when vascular engorgement is present. Under such circumstances there are also present the additional phenomena of the profuse exudation and hemorrhage. Erosion of an engorged mucosa can be expected to produce greater hemorrhagic manifestations than a similar process in a nonengorged mucous membrane. A clearer conception of these phenomena may result if one considers the engorged, devascularized segment as a large, blood-soaked sponge, which, by erosion of its surface membrane, decompresses itself by bleeding from the open pores of its mucosal capillaries. This concept is supported in our experiments by the constant finding of acid hematin in the contents of those stomachs showing engorgement and gastritis, while the contents of those stomachs in which gastritis and engorgement were minimal contained only clear fluid.

The predilection of gastritis in these experiments for the mucosa of the corpus, corroborates the findings of Afendulis and Gulzow. The reason may be that the mucosa of the antrum and *magenstrasse* in the dog is more firmly bound to the underlying muscularis and is more compact, permitting less engorgement of these areas. This selective distribution of edema and engorgement was evident in those control experiments in which the effect of engorgement alone was studied. In addition, the predominance of mucous cells in antral epithelium may afford a measure of protection against erosion in this area. These regional differences in structure are not so definite in the human, which may at least in part account for the "antral gastritis" described in specimens of the resected human stomach.

Time was demonstrated to be an important factor in these experiments. Reference to Table II shows that a minimum time-interval of 60 minutes between the commencement of devascularization and the examination of the

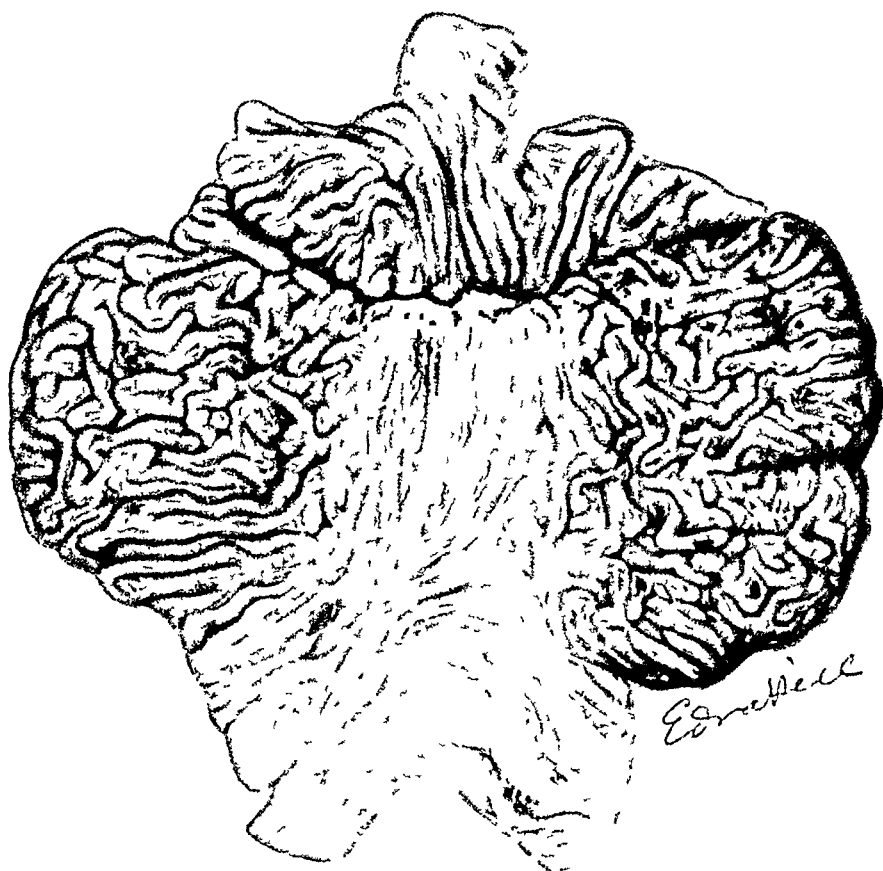


FIG 7—Dog's stomach excised *in toto*. Free hydrochloric acid introduced into both the distal and proximal compartments. Congestion only in distal compartment. Note distribution of engorgement and gastritis in distal segment, tending to avoid antrum and *magenstrasse*.

specimen was necessary for the appearance of gastritic changes in the engorged stomach, and that the maximum changes were reached in between 60 and 120 minutes

How far does the operation of subtotal gastrectomy, as performed in various clinics reproduce conditions of devascularization, engorgement, and time, which we found necessary for the production of gastritic change? The answer to this question resolves itself into an appraisal of the various features of the operative procedure which might contribute to the production of engorgement of the segment to be resected

The procedure of delivering the stomach from the abdominal cavity to facilitate resection, may at the same time increase gastric engorgement by hindering venous return. The placing of large gauze packs may likewise obstruct venous return by compression of the regional veins

By far the greatest cause of congestion, however, is most frequently found in the actual procedure of resection itself. The usual technic calls for careful ligation of all the blood vessels to the portion of the stomach to be resected, beginning at or near the pylorus, and proceeding toward the cardia. The left gastric vessels are usually the last to be ligated, after which a crushing or rubber-covered clamp is usually placed across the stomach at the level of the proposed resection. The procedure has the effect of progressively converting the distal portion of the stomach into a closed vascular sac, into which the left gastric artery has been allowed to pump blood for from 10 to 45 minutes, depending upon the speed of the surgeon and the actual technic employed

The time elapsing between the beginning of resection and the examination of the resected specimen is important. The actual time of resection may be short but the specimen may be relegated to a specimen basin for some time before examination. On the other hand the resection time may be prolonged, but the resected specimen may be examined promptly on removal. In both instances, the total time-interval may exceed the critical period for the appearance of gastritis, which we have shown in dogs to be 60 minutes. It is interesting to note that removal of the clamps from the cut surfaces of the resected specimen, or opening the specimen before a certain time has elapsed, allows vascular decompression of the viscus, and reduces the incidence of gastritis. One might expect, therefore, slightly greater congestion, and consequently more marked gastritis, if crushing clamps are used during the resection

SUMMARY

The incidence of gastritis reported from different clinics and from different countries varies widely. Schindler, and his coworkers, suggested that the gastritis observed was an artefact produced by the technic of gastric resection in the presence of free hydrochloric acid

In the present work it was demonstrated that when free acid was present in the stomach of the dog, gastric changes were (1) proportional to the

degree of gastric vascular engorgement which occurred during operation, and (2) to the time elapsed between beginning the resection and the examination of the specimen. The technic of gastrectomy as employed in surgical clinics can reproduce these conditions.

The present work seems to indicate that gastroscopy rather than the study of surgically resected specimens should be the basis for the evaluation of the frequency of the coexistence of peptic ulcer and gastritis.

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RUPTURE OF THE STOMACH FOLLOWING INGESTION OF SODIUM BICARBONATE

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SPONTANEOUS SUBCUTANEOUS RUPTURE of the stomach, unassociated with trauma of the abdominal wall or with preexisting pathologic lesions of the stomach itself, is an unusual and interesting condition. We frequently encounter rupture of the stomach as a result of perforating ulcers, and such injuries as gunshot or stab wounds or other direct localized trauma to the abdominal wall, and, for this group, understand the mechanism involved. We herewith present a case of spontaneous rupture of the stomach, review the literature on the subject, and discuss the possible mechanism of such a catastrophe.

Rupture of the stomach as a result of trauma to the abdominal wall, without a penetrating wound, is seen not infrequently, and N J Wolf¹ has reviewed 46 such cases. Rupture of a solid viscus (liver, spleen, pancreas, kidney) or of the small bowel, is not uncommon following severe crushing violence to the abdomen, but the stomach almost invariably escapes injury. It seems logical that the elastic, loosely-attached pliable walls of the stomach readily and rapidly accommodate the organ to the abrupt change in intra-abdominal pressure and configuration, and the gas bubble at the cardia does not exert sufficient counterpressure to cause a bursting rupture. The cardiac and pyloric orifices, too, permit an escape of the stomach contents and allow for a rapid decompression. Ritter² has done experimental work to support this contention by delivering repeated, forceful blows on the upper abdomen of dogs without producing a gastric rupture. Vanni³ showed that trauma over the overfilled stomachs of dogs produced only mucosal tears. In some cases, it is true, the human stomach may be torn at its attachments, but usually the sudden displacement and change of pressure is not sufficient to tear this flaccid and mobile organ. In most cases of traumatic rupture of the stomach, without abdominal wall penetration, the stomach was distended with food and gas. Filling, or overfilling, of the stomach produces a more or less fixed shape, reduces mobility and predisposes to rupture. Trauma at such a time, if there is sufficient distention and if the wall itself has undergone certain reversible changes which approach a pathologic state, will cause a tear in the wall of the stomach usually at or near the lesser curvature. Cardiospasm or pylorospasm must be considered as contributory factors since this would tend to deprive the stomach of their safety valve effect. Glassman⁴ points out that if the contents of the stomach can escape through the cardia or pylorus

the fatal increase in pressure at the moment of trauma can be avoided "The tonicity of these openings is controlled by a nervous mechanism which is not easily and suddenly overcome and may be increased by pylorospasm or cardio-spasm"

The mechanism of rupture without trauma, on the other hand, is somewhat more complex, and one is inclined to suspect mild trauma or an unrecognized pathologic lesion of the wall, especially ulcer. Most of the cases reported in the nineteenth century literature were probably not ruptures of the normal stomach, and Cruvillier's⁵ exposition of the condition, now easily diagnosed as perforated peptic ulcer (1832), did not clear the literature of these unreliable case reports until the latter part of the century. The progress of surgery, with opening of the abdomen, and more frequent postmortem examinations are responsible for an increase in our knowledge pertaining to this uncommon condition. It is also true that mild force can, under special circumstances, cause disruption of the stomach, and that mild trauma may be forgotten by the patient who is suffering severe peritoneal pain. Conversely, mild trauma may be coincidental or suggested to the patient.

The normal collapsed stomach, in a state of physiologic rest, is not subject to rupture. A traumatic rupture occurs as a result of overdistention. With progressive overfilling of the stomach, there first occurs a tonic physiologic relaxation. When the limits of this state have been reached, further additions to the gastric content cause overfilling, with an atonic stretched and thinned wall, and perhaps mechanical mucosal tears. Busch,⁶ on the other hand, believes rupture occurs more frequently with tonic rather than atonic dilations. With overdistention there is interference with the circulation of the gastric wall, and areas of softening occur. Talma,⁷ in rabbit experiments, showed that with overdistention areas of softening and infarcts are produced, and a small amount of HCl will cause ulcers and necrosis in such stomachs. These changes are probably reversible. Rupture occurs as a result of the mounting pressure from within exerted on the weakened and thinned wall. The final increment of pressure may be of a sudden nature and is probably gaseous due to rapid release of fermentation gases or from carbon dioxide after ingestion of sodium bicarbonate. Murdfield⁸ has shown that the sudden increase of gas pressure produced by adding some sodium bicarbonate to two or three liters of weak HCl will regularly produce ruptures of cadaver stomachs, or at least submucosal tears. (This observation is of particular interest since the case we report was precipitated by, or followed the ingestion of sodium bicarbonate.) The final increment of pressure may be from without the stomach, as in the case of traumatic ruptures, further emphasizing the pathophysiologic similarity of the two conditions. Miller⁹ reports a case of spontaneous rupture of the stomach during labor, in which the pressures of vomiting, straining, and a supporting Beck corset resulted in a three-centimeter ragged perforation at the midportion of the greater curvature. Vomiting was an "onset" symptom in several of the abstracted cases. Huttyra and Marek¹⁰ believe that rupture of the stomach may occur in horses from the

violent contracture of the gastric musculature Weiss and Mallory¹¹ report ten cases of laceration near the gastric cardia following alcoholism and vomiting, and believe that pressure changes in the stomach are responsible

In spontaneous ruptures pylorospasm and cardiospasm are probably present, which prevent the escape of the distending contents It is apparent that some factor must interfere with the normal emptying of the stomach, or emptying by emesis, or overdistention beyond the limits of elasticity cannot occur In this connection, it is interesting to note that many cases of gastric rupture have been reported, in which a pathologic lesion of the esophagus, pylorus, or duodenum served to block the pressure-releasing mechanisms and a spontaneous rupture occurred in a nondiseased area, apparently by the above described mechanism Among this type is a case reported by Cavaillon and Leriche¹² of a stenosing carcinoma of the pylorus After a heavy meal, a gastric lavage was attempted, resulting in a perforation in an undiseased area of the anterior wall near the lesser curvature Cannon and Halbert¹³ report the occlusion of a previously patent valvular stenosis of the duodenum, with acute dilation and rupture of the normal stomach A tear 1.5 cm was produced about 2 cm from the cardiac orifice Seegar and Shulz¹⁴ report a case of spontaneous rupture in an infant of 17 months At autopsy, an obstructing band was found 20 inches below the pylorus Wunschheim¹⁵ reports a case in a patient whose stenosing esophageal neoplasm prevented vomiting There was a tear two inches long from the cardia parallel to the lesser curvature Rupture of the stomach when incarcerated in a diaphragmatic hernia has been reported by Beraud and Gallois,¹⁶ and indicates that some damage or obstruction to the stomach's openings may have followed from its abnormal position These cases illustrate the fact that an obstruction to one or the other of the stomach's orifices is an important factor in the production of a gastric rupture

Oscar Glassman⁴ reports 14 cases of spontaneous rupture of the stomach Of these, two were operated upon, and one recovered The others died Wolf's¹ review, in 1936, lists 17 cases, some of which are from Glassman's series We have found 13 additional cases which can definitely be considered spontaneous ruptures of the stomach This makes a total of 30 cases to which we add the one herewith reported Of these 31 cases only five were operated upon There were two recoveries Since 1911, there has been no such case admitted to the Jefferson Hospital in Philadelphia However, there have been two cases of spontaneous rupture of lower end of the esophagus, near the cardia, which revealed no existing pathologic lesion at post-mortem One similar case was found among the records of the Philadelphia General Hospital, covering the records for the past five years

Pathology—The rupture of the gastric wall usually occurs on the lesser curvature A number of the cases reported do not specifically locate the site of the tear As Key-Aberg¹⁷ points out, with distention the stomach tends to assume a spherical shape Therefore, the lesser curvature is stretched most

and tears first Cavaillon and Leriche¹² advance a similar explanation and demonstrate this localization of tears on dogs Frankel¹⁸ believes the absence of mucosal folds on the lesser curvature plays a rôle A second common site is the anterior wall near the fundus The tears present clean edges, vary in length, and may extend into the esophagus At operation or postmortem the stomach is usually found to be greatly distended and there is gross contamination of the peritoneal cavity with undigested and partially digested food and liquids Microscopic study of the gastric wall shows thinning, capillary hemorrhages, and early muscular degeneration

Clinical Picture—The patient presents the picture of an overwhelming abdominal catastrophe There is often a history of dietary or alcoholic debauchery The patient may or may not describe a sudden onset of pain In some cases a sensation of "giving way" or a "bursting noise" has been heard¹⁹ Shock and prostration predominate, the abdomen has a peculiar rigidity and diffuse tenderness, and peristalsis is absent Subcutaneous emphysema was noted in a number of the cases This was true of each of the three cases of spontaneous rupture of the lower end of the esophagus mentioned, and accompanied those cases of spontaneous rupture of the stomach in which the tears extended into the esophagus, and which were due to migration of gastric gases into the mediastinum

Diagnosis—This has not been made preoperatively in any case of spontaneous rupture of the stomach However, the diagnosis of ruptured esophagus was confirmed at autopsy in one case Of the 31 cases reviewed, only five were operated upon, and two recovered Though the course is usually one of rapid death from generalized peritonitis, in two cases there was spontaneous recovery, with abscess and fistula formation

Case Report—G K, white, an obese female, age 51, weighing 220 lbs, was admitted to the Philadelphia General Hospital, July 29, 1939, at 12 05 A M She had been overeating and drinking alcoholic beverages since July 21, 1939 On July 26, 1939, she suffered vague upper abdominal pains but was relieved by vomiting On July 28, before dinner she had "several drinks" and then ate a "very heavy" meal of macaroni, meat balls, cheese, tomatoes, potatoes, bread, pie, water and three glasses of grape juice A little later she drank some whisky She began to feel quite bloated and had "heavy feelings" in her abdomen To relieve this she took "several teaspoonsful of sodium bicarbonate in a glass of water and drank it down" Immediately after this she felt a sudden, severe, generalized abdominal pain which "doubled her up" It continued unabated, with periods in which the pain was referred to the right shoulder She vomited repeatedly up to the time of her admission, the vomitus containing small quantities of blood mixed with fluids and particles of food

On examination, she appeared in shock, pulse 140, respirations 32 and were shallow and rapid, temperature 99° F Blood pressure 138/96 She was doubled up with pain, and her forehead was beaded with a cold perspiration The right breast was absent (amputated in 1930 for cyst) The heart was essentially negative The lungs were normal There was generalized tenderness of the abdomen with corresponding rigidity The rigidity was somewhat less than the "board-like" character seen in perforated ulcer Peristalsis was absent throughout, though the patient's uncontrolled grunting made this observation difficult A large mass which we thought to be a large uterine myoma was present in the lower abdomen

SPONTANEOUS RUPTURE OF STOMACH

Leukocyte count was 14,900, 74 per cent polymorphonuclear neutrophils, 22 per cent lymphocytes, 3 per cent mononuclears, and 1 per cent eosinophils. Blood urea nitrogen 17 mg per cent. A flat film of the abdomen showed that "there apparently is considerable air under both diaphragms. The stomach appears considerably dilated and distended with gas, and there are several loops of colon with gas demonstrable. No evidence of acute obstruction."

In an effort to improve the patient's condition preoperatively, treatment was instituted which consisted of Wangensteen suction-drainage of the stomach and intravenous administration of glucose in normal salt solution. In spite of this, she grew rapidly



FIG 1—A diagrammatic drawing to show the distended stomach and the greatly distended lesser peritoneal sac. An overflow is noted through the epiploic foramen.

worse so that her temperature was 104° F at 2 P.M., at which time her abdomen was opened under continuous spinal anesthesia²⁰. It was then approximately 14 hours after her admission, and about 12 hours after air had been demonstrated in the peritoneal cavity. In retrospect, we must condemn the delay in bringing this case to operation, for this case represents an example of inexcusable postponement of operative treatment while waiting for improvement in the general condition to be brought about by use of the Wangensteen tube and other conservative measures. While the patient presented an obscure and confusing diagnostic problem, it is now obvious that her chances of recovery would have been greatly enhanced had operation been undertaken soon after her admission.

On opening the abdomen large quantities of partially digested food were found present throughout the greater and lesser peritoneal sacs. The gastrohepatic omentum was greatly distended (Fig 1), and seemed to confine most of the gastric contents to the

lesser sac This may explain the peculiar rigidity noted on the first examination The gastrohepatic omentum was opened and the free fluid and particles of food were aspirated (3.5 liters) and wiped from the greater and lesser sacs of the peritoneal cavities A tear, approximately five inches long, was found situated on the lesser curvature (Fig 2) It involved the lower one and one-half inches of the esophagus and ran downward toward the pylorus No evidence of any pathologic lesion in the stomach or esophagus could be found The laceration was closed with considerable difficulty, and the suture line re-

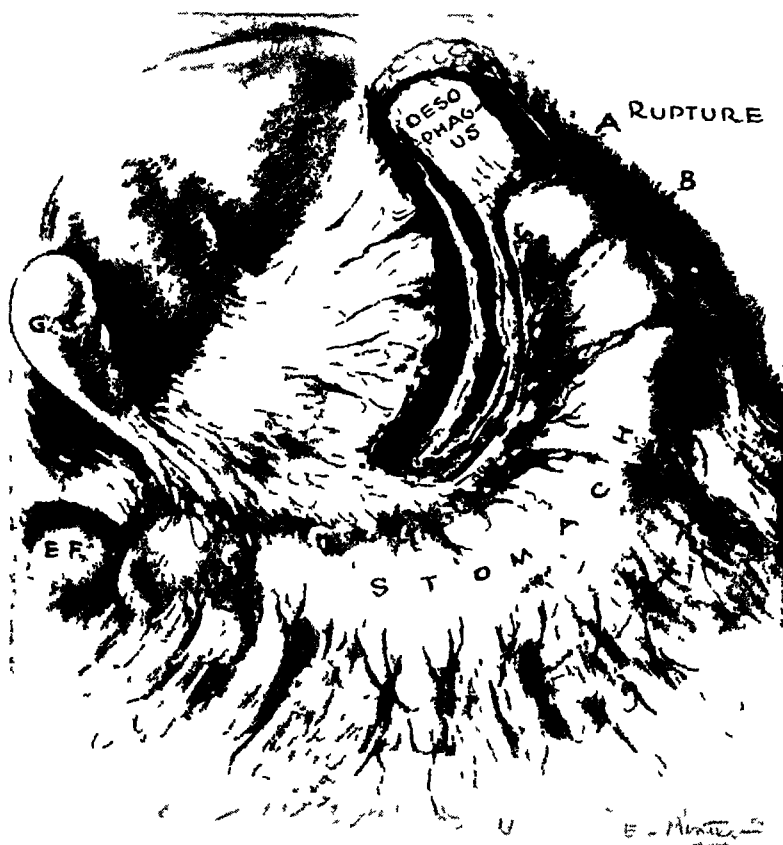


FIG 2—A drawing showing the cut gastrohepatic omentum, exposing the lesser sac, and the rupture involving the lower end of the esophagus and extending along the lesser curvature

enforced with the divided gastrohepatic omentum A cigarette drain was placed in the lesser peritoneal cavity and two cigarette drains were carried out through a stab wound in the suprapubic area During the operation, the patient received a transfusion of 400 cc of citrated blood She left the operating table with a blood pressure of 110/70, pulse 125, respirations 25 Toxemia and peritonitis progressed rapidly and the patient died six hours after operation, approximately 24 hours after the onset Permission for autopsy was refused

SUMMARY

(1) A case of rupture of the stomach following the ingestion of sodium bicarbonate is submitted, with a review of the material found on spontaneous rupture of the stomach

(2) Rupture of the healthy stomach is an unusual condition It has not been diagnosed preoperatively or before autopsy

(3) The factors concerned with the possible mechanism of this catastrophe are discussed

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PRELIMINARY COLOSTOMY IN THE MANAGEMENT OF GASTROCOLIC AND GASTROJEJUNOCOLIC FISTULAE

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AT A MEETING of the American Surgical Association in May, 1939, Pfeiffer,⁸ of Philadelphia, and Kent, of Norwich, reported a method of handling patients suffering with gastrojejunocolic fistulae which throws a new light upon the pathologic physiology of this condition, and suggests the possibility of lowering the high mortality of surgical treatment. They happened upon this procedure almost by accident. One of their patients who had a gastrojejunocolic fistula was given a barium meal which failed to pass from the stomach into the colon. However, barium given by enema passed readily into the jejunum and stomach, demonstrating a ball-valve type of fistula. At operation, the fistula was found to be surrounded by dense adhesions and marked inflammatory reaction. It was decided to perform a preliminary colostomy, on the theory that since the flow through the fistula was in one direction only, namely, from colon to stomach, a colostomy would divert the fecal stream and make subsequent operation upon the fistula easier. After an ascending colostomy was performed the diarrhea ceased entirely, and the patient picked up surprisingly in weight and strength. This was not in accord with the accepted theories regarding the cause of diarrhea in these cases, namely, that it is due to the emptying of acid stomach contents into the colon. Rather, it would appear that regurgitation of colonic contents into the upper gastro-intestinal tract sets up a severe enteritis and consequent diarrhea. A few months later, at operation, the inflammatory reaction around the fistula was found to have subsided almost completely, the tissues were in more nearly normal condition, and the operation for correction of the fistula was carried out more simply than it could have been previously. After simple closure of the gastro-enterostomy, colonic and jejunal fistulae, the patient made an uneventful recovery. The colostomy was closed at a later date. These authors reported one other patient of their own and one of Dr. Ralph Colp's, both with similar courses following preliminary colostomy. Our interest in this subject began in September, 1939.

ILLUSTRATIVE CASES

Case 1—V. S., white, male, age 59, entered the San Francisco Hospital, May 13, 1936, complaining of continuous vomiting of foul material for two months, diarrhea with as many as 16 bowel movements daily, and loss of 50 pounds in weight. He had had a posterior gastro-enterostomy in May, 1930, for a persistent duodenal ulcer. He was well for two years following the gastro-enterostomy when he suddenly experienced severe epigastric pain lasting about 24 hours associated with abdominal tenderness. Subsequently

there occurred nocturnal diarrhea, and he noted large amounts of undigested food in the stools, followed by extreme weakness and a loss of 50 pounds in weight. A gastro-jejunal fistula was demonstrated by barium enema.

Operation—June 11, 1936. The fistula was found and was repaired by dissecting the colon free from the gastro-enterostomy and closing the fistulous openings in the colon and in the jejunum. The patient was left with the original gastro-enterostomy. After a stormy convalescence he was free from diarrhea but continued to have marginal ulcer symptoms, regardless of diet.

Upon reentry to the San Francisco Hospital in September, 1939, he weighed 97 pounds (his best weight had been 180 pounds). Physical examination revealed a pallid, dehydrated, markedly emaciated adult male with evidence of generalized arteriosclerosis. Peristalsis was hyperactive visually and audibly. There was an old healed upper midline scar extending from the xiphoid to the umbilicus. There was a healed right inguinal scar and a McBurney incision scar which herniated with increased intra-abdominal pressure. Urinalysis, complete blood chemistry, blood Wassermann and Kahn were negative. Examination of the blood at first showed evidence of marked dehydration and later a mild secondary anemia. Barium enema revealed a fistulous communication between the mid-portion of the transverse colon and jejunum which filled the stomach and jejunum with barium simultaneously. Gastroscopic examination did not disclose the fistula. Barium by mouth emptied through the gastro-enterostomy and passed from the jejunum into the colon.

First Operation—On October 10, 1939, the cecum was brought out of the abdomen, and was opened on October 11. With the opening of the cecostomy the diarrhea immediately stopped. Charcoal given by mouth appeared in the cecostomy after 15 hours. The patient began to gain weight and strength immediately and all vomiting stopped. Barium by mouth, October 30, 1939, 20 days following the cecostomy, revealed the gastrojejunal fistula, and so did a barium enema given December 29, 1939, two months later. The patient gained from 97 pounds upon entry to 131 pounds in less than two months. All of the patient's symptoms had disappeared.

Second Operation—January 16, 1940. Under cyclopropane anesthesia, the upper midline abdominal scar was excised and the abdomen opened. There were many adhesions. The stomach was found to be large and dilated, the duodenum was very narrow, fibrous and contracted, measuring less than 1 cm in diameter. Palpating through the stomach wall, a stoma could be felt between the stomach and a loop of proximal jejunum and also between the transverse colon and jejunum. The inflammatory changes usually found about this type of lesion were completely absent. A jejunal fistula measuring about 3 mm in diameter was found. The colon was dissected free and closed transversely with chromic sutures. The gastro-enterostomy was taken down and, after resection of three-quarters of the stomach, a Polya type of posterior anastomosis was made, using the combined opening in the jejunum left by the previous gastro-enterostomy and jejunal fistula. The patient made an uneventful recovery. On February 13, 1940, the cecostomy was closed. The patient has since remained well.

Case 2—W. A., white, male, age 42, entered the San Francisco Hospital, January 2, 1940, complaining of severe pain in the epigastrium relieved by vomiting of fecal material and belching of gas with fecal odor, both of two months' duration. During the past month he had had five to six liquid bowel movements daily, and had lost 17 pounds in weight. He was so weak he could not walk. From the age of 14 he had suffered with stomach trouble, characterized by burning epigastric pain and sour eructations relieved by soda. In 1923, a gastro-enterostomy was performed in the Buffalo City Hospital. He was well for one year after which his symptoms returned. In 1932, 1934, and in 1937 he had suffered with severe gastric hemorrhages, requiring transfusions.

Physical Examination—The patient was markedly emaciated, and his fingers were slightly clubbed. The breath was very foul. The thorax was poorly nourished, with poor expansion of both sides. There was impaired resonance over both apices. Both bases were hyperresonant. No râles were heard. Blood pressure 120/80. Heart negative. The

abdomen was scaphoid, with an oblique right upper quadrant scar and a transverse right lower quadrant scar. Both upper quadrants were slightly rigid and tender to pressure, especially on the left. Peristalsis was markedly hyperactive. *Laboratory Data* Blood chemistry negative. Mild secondary anemia. Blood Wassermann and Kahn negative.

Gastroscopic examination revealed an atrophic gastric mucosa. No pyloric activity was seen. The gastro-enterostomy could not be seen. A barium meal, January 8, 1940, revealed a gastrojejunal fistula. Methylene blue given by mouth appeared in the stool after one hour and 30 minutes. Gastric analysis disclosed a complete absence of free HCl, and a highest total acid of 20° at ten minutes. On January 13, 1940, the gastro-colic fistula was demonstrated by barium enema.

First Operation—Under local anesthesia, a loop-colostomy was performed on the right side of the transverse colon, which was opened in bed a few days later. The diarrhea stopped immediately following the opening of the colostomy. In spite of an advanced bilateral pulmonary tuberculosis this patient gained 18 pounds after the colostomy was performed.

Second Operation—August 1, 1940. Under spinal anesthesia, the abdomen was opened through a left paramedian upper abdominal incision. Although many adhesions were encountered, there was a remarkably small amount of inflammatory reaction about the old gastro-enterostomy. A small fistula was found connecting the anterior margin of the gastro-enterostomy opening and the posterior wall of the colon. The colon was freed and the fistulous opening closed with chromic gut. The gastro-enterostomy was taken down and the opening in the jejunum closed with chromic catgut. A gastric resection was then performed, removing about three-quarters of the stomach.

In spite of the fact that this patient was suffering with an extensive pulmonary tuberculosis, the postoperative course was not remarkable. On the fourth postoperative day he started taking nourishment by mouth, and after the sixth postoperative day he remained afebrile. The abdominal wound healed by first intention.

Because of some difficulty experienced with the colostomy in this patient, we were able to observe the influence of stool in the distal segment of the colon upon the frequency of bowel movements both by rectum and colostomy. Whenever the distal segment of colon was free of stool the diarrhea stopped. This seemed to us to be rather conclusive proof that Pfeiffer was right in his contention that the diarrhea in these patients was not due to gastric contents getting into the colon but rather due to colonic contents regurgitating into the upper gastro-intestinal tract causing hyperperistalsis in the small bowel and consequent diarrhea. The fact that methylene blue taken by mouth appeared in the stool after one hour and 30 minutes would also make one believe that it had passed through the gastro-intestinal tract very rapidly rather than directly from the stomach into the transverse colon.

Case 3—J. D., white, male, age 39, entered the San Francisco Hospital, January 31, 1940, complaining of diarrhea of two months' duration. In 1929, he had had a sudden severe onset of epigastric pain and was operated upon for a perforated peptic ulcer. A gastro-enterostomy was performed and the ulcer was closed. Since that time the patient suffered with continuous ulcer symptoms. In 1938, he reentered the hospital and a marginal ulcer was demonstrated but he was not operated upon. About two months before his last entry a diarrhea suddenly developed which gradually increased in severity. With the onset of diarrhea all pain disappeared but he began to belch fecal-smelling gas and had occasional attacks of vomiting.

Physical Examination—The patient was thin and pallid, with a scaphoid abdomen which showed two celiotomy scars. Peristalsis was violently hyperactive. Barium enema

revealed a gastrojejunocolic fistula. Barium meal failed to demonstrate the fistula but showed very rapid filling of the small bowel both through a gastro-enterostomy opening and through the pylorus. The barium was seen to enter the large bowel after 30 minutes.

First Operation—February 3, 1940. A loop-colostomy was established in the right side of the transverse colon, which was opened in bed four days later. The diarrhea stopped immediately following the opening of the colostomy. Five weeks after the colostomy the patient had gained from 103 pounds to 119½ pounds.

Second Operation—March 21, 1940. The abdomen was opened through the old mid-line upper abdominal incision. Many adhesions were encountered but the region of the gastrojejunocolic fistula was remarkably free of inflammatory reaction. A very large fistulous opening was found between the jejunum and colon, apparently beginning at the margin of the gastro-enterostomy. The opening in the large bowel measured about 5 cm. The colon was dissected free and closed transversely with chromic sutures. The gastro-enterostomy was then taken down and, after resection of about three-fourths of the stomach, a posterior Polya type of anastomosis was made, using the original opening in the jejunum for the anastomosis. An old healed scar of a marginal ulcer was removed from the edge of the opening in the jejunum before the anastomosis was undertaken.

This patient did well following the resection, with the exception that the proximity of the colostomy to the midline wound caused some infection and delayed healing. On April 5, 1940, about two weeks following the gastric resection, a barium enema revealed some narrowing of the transverse colon at the site of the previous fistula. Barium flowed from the superior margin of the distal end of this narrowed segment into what appeared to be a sinus tract leading upward toward the greater curvature of the stomach, but no barium entered the stomach.

Third Operation—May 23, 1940. The colostomy was closed.

This patient demonstrated three important points. First, that barium given by mouth passes very rapidly through the irritated small bowel; second, that even though some leakage may occur from the site of repair in the colon, preliminary colostomy will prevent disaster from this leakage, and third, that diarrhea will occur in these patients even though a fistula cannot be demonstrated by giving barium by mouth.

In their original article reporting this procedure, Pfeiffer and Kent mentioned that upon reviewing the literature a single instance was found in which colostomy was employed as a preliminary measure to the correction of gastrojejunocolic fistula. *viz.*, Colucci⁴ reported a cecostomy performed upon a patient with symptoms suggesting intestinal obstruction. A gastrocolic fistula was later demonstrated, and was apparently the result of spontaneous perforation of a gastric ulcer into the colon. The symptoms of bowel obstruction in this case brought to mind a patient seen at the San Francisco Hospital in October, 1938. He had been transferred to us from another hospital where he had undergone an appendectomy because of vague gastro-intestinal symptoms, with local findings suggesting appendicitis. The appendix was found to be normal but the cecum was indurated at its base, suggesting a previous rupture, with abscess formation. Following appendectomy there developed generalized peritonitis and, later, intermittent attacks of bowel obstruction and a left lower quadrant abscess. The abscess was drained. A fecal fistula developed in the appendectomy wound and in that following drainage of the abscess. At no time did this patient have diarrhea. Three

days after entry to the San Francisco Hospital a gastrocolic fistula was demonstrated, both by barium enema and with barium given by mouth. Tissue removed from the walls of the fecal fistulae showed tuberculous granulation tissue and tubercle bacilli. Roentgenologic examination of the chest revealed bilateral pulmonary tuberculosis, with cavitation. The patient died in the Tuberculosis Division about three months after entry, without ever experiencing diarrhea.

Autopsy revealed an opening in the greater curvature of the stomach, about 5 mm in diameter, which communicated with a sinus tract leading to a circular opening in the transverse colon. The sinus tract also communicated with two other openings into the colon, one into the transverse colon about 4 cm from the first opening and the other into an ulcer in the cecum about 4 cm above the ileocecal valve.

The absence of diarrhea in this case led us to study other gastrocolic and gastrojejunocolic fistulae in the records of the San Francisco Hospital. We were able to find the histories of six instances of gastrojejunocolic fistulae, all secondary to marginal or jejunal ulcers perforated into the transverse colon. These all occurred from two to 15 years after a gastro-enterostomy. In all of these patients, as in the three reported, the outstanding symptoms were diarrhea, and loss of weight and strength.

One of these patients had a gastro-enterostomy performed in 1915. He was well until 1923, eight years later, when he entered the University of California Hospital complaining of severe diarrhea and loss of weight and strength. A gastrojejunocolic fistula was demonstrated and repaired at operation by taking down the gastro-enterostomy and restoring the normal continuity of the bowel. The patient was well for one and one-half years when all of his original ulcer symptoms reappeared. Six months later he entered San Francisco Hospital complaining of pain in the abdomen and belching of foul-smelling gas. He had no diarrhea. Barium by mouth revealed a gastrocolic fistula. The small bowel was not involved. This patient had a gastrojejunocolic fistula at one time associated with a severe diarrhea and later a gastrocolic fistula with no diarrhea.

Six other cases of interest were reviewed. One case of rupture of a carcinoma of the stomach into the transverse colon, one carcinoma of the transverse colon into the stomach, and one gastrocolic fistula secondary to an abdominal abscess following trauma to the upper abdomen. In all of these cases a gastrocolic fistula was demonstrated roentgenologically, and in two, confirmed at autopsy. All three patients complained of belching of foul-smelling gas and of fecal vomiting, in none was a diarrhea present.

The other three cases reviewed, represented enterocolic fistulae, two carcinomata of the colon with rupture into the small bowel, and one carcinoma of the ileum ruptured into the large bowel. In all three of these patients, violent diarrhea was the outstanding symptom after the fistula had become established. In one patient the symptoms were those of a bowel obstruction.

until the fistula appeared six days after entry into the hospital. Diarrhea was followed by relief of pain and vomiting.

Although diarrhea is said to be an outstanding symptom of gastroduodenal fistula, a review of the cases reported in the literature would cast some doubt upon this contention. It is true that certain cases reviewed had diarrhea as an outstanding symptom but in most of these, the gastroduodenal opening was very large or there was some obstruction to the normal flow of gastric contents through the pylorus. In a large number of the case histories reviewed, constipation rather than diarrhea was the rule. On the other hand, gastrojejunocolic fistulae and enterocolic fistulae in which a segment of small bowel is present and patent distal to the fistulae, diarrhea is invariably present.

These facts would tend to indicate that the low threshold of irritability of the small bowel has something to do with the development of diarrhea in these patients, and certainly tends to disprove the popular idea that the emptying of stomach contents into the large bowel is the etiologic factor. At any rate, there can be little doubt that short-circuiting the fecal stream, proximal to the fistulous opening, promptly alleviates all of the symptoms and restores the patient to normal health.

It is not the author's purpose here to discuss the choice of procedure after colostomy except to say that our review would indicate that simple restoration of continuity is frequently followed by return of the original ulcer symptoms and that simple closure of the colonic fistula is apt to lead to recurrence. Preliminary colostomy makes any subsequent procedure simpler and safer and, as indicated by the first three patients reported here, allows one to undertake extensive gastric resection.

SUMMARY

(1) Nine cases of gastrojejunocolic fistulae have been studied together with four cases of gastroduodenal fistulae and three cases of enterocolic fistulae.

(2) Three cases of gastrojejunocolic fistulae treated by preliminary colostomy are presented in detail.

CONCLUSIONS

(1) Colostomy as a preliminary procedure in the treatment of gastrojejunocolic fistulae not only stops the diarrhea immediately and completely, allowing the patient to regain his body weight and normal fluid balance, but greatly facilitates the surgical correction of the fistula at a subsequent operation by correcting the inflammatory reaction usually seen about these fistulae.

(2) The diarrhea experienced in gastrojejunocolic fistulae is, definitely, the result of a reflux of colonic contents into the upper gastro-intestinal tract, rather than the influx of gastric contents into the large bowel.

(3) Diarrhea is a symptom of gastrojejunocolic fistula but not necessarily a symptom of gastroduodenal fistula.

(4) Right-sided transverse colostomy, in our experience, is preferable to cecostomy in these patients.

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THE SURGICAL MANAGEMENT OF FECAL FISTULAE

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THE DEVELOPMENT of a fecal fistula following an abdominal operation is a source of great embarrassment to the surgeon and of considerable distress to the patient. This unfortunate complication is probably less common now than was once the case,² because of an increasing tendency to avoid operating for acute pelvic inflammatory conditions and because of a better understanding of such diseases as diverticulitis and regional enteritis. Yet it is still of sufficiently frequent occurrence to warrant an occasional appraisal of the methods employed in its management.

Recent progress in the care of patients having fistulae has been mainly in the field of conservative treatment. This phase of the problem has recently been reviewed by Dixon and Deuterman.¹ The main objectives of conservative treatment are to provide nature with every opportunity to bring about spontaneous healing, or, this failing, to get the patient into the best possible general condition before subjecting him to more heroic measures. Disturbances resulting from loss of fluids, electrolytes or enzymes, and nutritional deficiencies are recognized and corrected. Acute inflammatory processes are allowed to subside, and the condition of the tissues surrounding the fistula is improved as much as possible.

In this study we have attempted to evaluate the results of surgical treatment and to determine the factors influencing these results. As a basis for this study, the records of patients presenting themselves at the Mayo Clinic, between January 1, 1930, and December 31, 1934, inclusive, in whom an abnormal communication existed between the small or large intestine and the surface of the body, have been reviewed. Excluded were patients with anorectal fistulae or cases in which enteric stomata had been established purposely, in the course of stage-operations or for the relief of ileus.

It is generally stated that the greater the length of a fistulous tract, the greater the likelihood that spontaneous healing will take place. However, it is also true that the longer the tract, the greater the technical difficulties which may confront the surgeon, should operation prove necessary. This is well exemplified by the comparative simplicity attending repair of so-called "lip-fistulae"³ (short tract fistulae in which continuity between skin and mucous membrane exists) in contrast to correction of the more complex fistulae of other types. One hundred and fifty-five cases of the latter were encountered in the five-year period embraced by this study. One hundred and twenty-eight of these patients were subjected to operation.

TABLE I
CAUSATION OF 155 FECAL FISTULAE

Underlying Disease Process or Condition for which Operation Was Performed	Cases in which Closure Was Carried Out at the Mayo Clinic	Cases in which no Operative Attempt at Closure Was Made at the Mayo Clinic
1 Appendiceal disease		
A Appendicitis	36	8
B Conditions resulting from appendicitis	5	1
2 Benign disease of the female pelvic organs	22	3
3 Tuberculosis (intestinal or pelvic)		
A Definite	15	2
B Questionable	3	4
4 Malignant tumors		
A Intestinal	13	1
B Pelvic	0	2
5 Inflammatory disease of the bowel		
A Regional enteritis	11	0
B Ulcerative colitis	4	0
C Actinomycosis	0	1
6 Diverticulitis	6	3
7 Miscellaneous		
A Obstructive conditions of the bowel	5	1
B Intestinal perforation (gunshot traumatic)	4	0
C Affections of the spleen	2	0
D External hernia	1	1
E Cholecystitis	1	0

In Table I the fistulae are classified according to cause. Fistulae were most common following operations for appendicitis, appendiceal abscess, or conditions resulting from appendicitis (ileus, adhesions). Operations upon the female pelvic organs contributed the second largest number of fistulae. No fistulae occurred spontaneously, but in ten cases the only operation performed was drainage of an abscess secondary to rupture of an infected diverticulum, to perforation of an area of regional enteritis, or to pelvic inflammatory disease. There were no fistulae of congenital origin.

The operation which had resulted in the formation of a fistula was not a reliable criterion of the true nature of the underlying disease. Thus, of 67 cases in which appendicectomy had been performed, tuberculosis was found in seven, regional enteritis in four, malignant lesion in three, and diverticulitis in two.

In 11 cases fistulae had been present less than three months before the patient was admitted. In 26 cases the duration was between three and six months. The greatest number of fistulae (45) had been present between six months and one year. In 30 cases the duration was between one and two years, in 18, between two and five years. In 25 cases the fistulae had been present for more than five years. Included were one case of 45 years' duration, and three of more than 20 years' duration.

As would be expected from the preponderance of appendiceal disease as an etiologic factor, the right lower quadrant was the most common site of the external opening, with the low midline scar of previous pelvic operation occupying second place, and the left lower quadrant, third place. No portion of the abdomen, groins or loins escaped as a site of opening. In four cases fistulae existed in the wounds of posterior resection of the rectum, and in one

case fecal matter (and urine) drained from a perineal fistula. Multiple external openings were present in 21.9 per cent of the cases. The size of the opening was too small to admit a finger tip in the majority of the cases, but in almost one-fourth of the cases a larger opening existed. The most common type of drainage was a scant but unmistakable fecal discharge, while in about one-fourth of the cases which came to operation, between 25 and 75 per cent of the feces passed through the fistula. In four cases no fecal matter passed through the normal channels. In a few cases, only pus was discharged.

In 27 cases operative closure was not attempted, because of disinclination on the part of the patient, of some serious contraindication, or of a desire to allow further time for spontaneous healing. These cases will receive no further consideration in this study, and all references hereafter will be to the cases in which operation was performed.

The most common site of the internal opening was in the ileum, 40 cases (31.3 per cent). In 20 (48.8 per cent) of the postappendiceal cases, the opening was in the cecum or what remained of the appendix, but in 15 cases (36.6 per cent), in many of which secondary operations had been performed, the ileum was involved. In 39 cases (30.5 per cent) the sigmoid was the site of the internal opening, pelvic operations accounting for 40.0 per cent of these, diverticulitis for 17.1 per cent, and tuberculosis, regional enteritis, appendicitis and malignant lesions accounting for the remainder. The jejunum was involved in two cases, the ascending colon in one, the transverse colon in two, the splenic flexure in two (following operations upon the spleen), and the descending colon in three. In 25 cases the site of the internal opening was not accurately localized.

Single openings were found in 67 cases (52.3 per cent) and multiple openings in 36 cases (28.1 per cent). Additional complicating internal fistulae existed in a number of cases—enterocolic fistulae in two cases, enterovesical fistulae in four, and in two cases there were openings communicating with the vagina. The complexity of some of the fistulae was truly remarkable. In one case fistulae in the cecum, sigmoid and ileum opened into a common tract, in another there were holes in the sigmoid, transverse colon and cecum. In one case, in addition to multiple ileal fistulae, the sigmoid was found to be completely divided. Most of the complex fistulae occurred in cases in which there had been previous attempts at closure.

In a considerable number of cases it was possible, preoperatively, to establish fairly accurately the location of the internal opening. In five cases sigmoid openings were visualized proctoscopically. Injection of radiopaque substances into fistulae or administration of barium sulphate with subsequent roentgenologic study established the presence of fistulae in several doubtful cases, and the segment of bowel involved in many. Multiple internal openings were not well demonstrated by these methods. Roentgenologic study was most valuable in detecting underlying diseases of the bowel and in supplying information regarding the patency of the bowel distal to the fistula.

Many of the patients were very poor operative risks. Debility was most

marked in the cases in which there was colitis or regional enteritis, but it figured prominently in almost 20 per cent of the cases. Many of the patients were emaciated, anemic and bedridden at the time of admission. Marked excoriation of the skin or inflammation of the tissues surrounding the fistula was present in about 10 per cent of the cases. Partial intestinal obstruction existed in five cases. Pelvic abscesses were very common. Pulmonary tuberculosis was present in seven of the 18 cases of tuberculous origin. Intestinal parasites were discovered in three cases. Unrelated conditions, such as obesity, hypertension, nephrosis, diabetes, rheumatic endocarditis and neurologic disorders added to the risk in other cases. Previous operative attempts at closure, varying from simple extraperitoneal suture to complex resections, had been performed in 49 cases (38.3 per cent).

Preoperative preparation was carried out along the lines described by Dixon and Deuterman. Intraperitoneal vaccine was administered to a number of the patients, a practice since discontinued in such cases, in which there has obviously been ample autovaccination.

OPERATIVE PROCEDURES

Curettage and Packing—This was carried out in 14 cases (10.9 per cent). Appendiceal, tuberculous, malignant and pelvic cases were represented in this group. When possible, multiple external openings were converted into single openings. In one case a foreign body was removed.

Extraperitoneal Closure—Simple freeing of the stoma with inversion of the mucosa and closure of the skin, without entering the peritoneal cavity, was carried out in only five cases (3.9 per cent).

Intraperitoneal Closure—This was the most commonly employed procedure, 47 cases (36.7 per cent). Diseased pelvic organs and appendixes, when present, were removed at the same time, abscesses were drained. In four cases short-circuiting operations, and in three cases proximal enterostomies were added for safety. In about one-fourth of the cases in which intraperitoneal closure was performed, such large defects in the wall of the bowel were present that simple closure by purse-string or transverse suture was not feasible and plastic procedures were required. Closure was usually effected with two or three layers of continuous catgut, silk occasionally serving in the outer layer. In most cases the abdomen was entered through the old incision, the fistulous tract being dissected out in the process, but in a few instances a new and remote incision, as recommended by Lockhart-Mummery,⁴ was employed. Drains were left in the peritoneal cavity in about half of the cases. In the few instances in which the fistulous tract was not removed it was utilized for drainage, and in a few cases subcutaneous drains were employed. In the remainder, no drains were inserted.

Resection—This was the second most commonly used procedure, 33 cases (25.8 per cent). It was the operation most frequently performed upon patients with regional enteritis or ulcerative colitis. Simple resection and anastomosis were performed in one-third of the cases in which this type of opera-

tion was carried out, while in another third, proximal enterostomy was added. In half of the remaining cases, stage resections were carried out, while in the remainder, leaking bowel stumps (left after previous resection) or previously short-circuited segments of bowel were removed. In a number of the cases repair of defects in other portions of the bowel was required.

Exteriorization—Obstructive resection or simple exteriorization was performed in five cases (3.9 per cent), simultaneous closure of openings in other parts of the bowel being carried out in several cases. Subsequent closure of the operative stoma was performed in three of the five cases in this group.

Appendicectomy—This was the only procedure carried out in four cases in which the fistula was ascribed to previous appendiceal disease.

Diversion Operations—Fistula-bearing segments were short-circuited in three cases, in one case a previously short-circuited segment was further isolated by division of the bowel proximal to the fistula-bearing portion, and in six cases colostomy was performed proximal to the fistulous bowel.

Pelvic Operations—Removal of pelvic organs affected by inflammatory disease was the operation performed in three cases, while in one case tuberculous pelvic organs were removed. In these cases either the opening in the bowel was not visualized or the condition of the surrounding tissues was felt not to warrant closure or resection.

Drainage of Intra-abdominal Abscess—This was performed in three cases.

Exploration—This was performed in three cases.

POSTOPERATIVE HISTORY

The average length of stay in the hospital of the 128 patients was 35 days. There were 13 postoperative deaths, a mortality rate of 10.2 per cent. In 28 cases (24.3 per cent of the 115 cases in which the patients lived) the wound was healed at the time the patient was discharged. In 60 cases (52.2 per cent of 115 cases) a seropurulent discharge persisted. In 27 cases (23.5 per cent of 115 cases) fecal matter was being discharged from the wound. Two of the healed wounds broke down after the patient left the hospital. Thirty-five of the wounds which were draining pus were subsequently reported healed, while four of those from which fecal matter was draining subsequently healed. There was no adequate follow-up on 23 patients (18.0 per cent of 128 cases), but in seven of these the wounds were healed at the time of discharge. A striking commentary on the seriousness of the condition is the fact that 16 more patients (12.5 per cent of 128 cases) died within one year of their departure.

Immediate postoperative complications included shock (seven cases), general peritonitis (ten cases), local peritonitis with abscess formation (five cases), severe wound infection (16 cases), erysipelas (one case), wound disruption (two cases), ileus (ten cases), pulmonary complications (ten cases), urinary fistulae (three cases), fecal fistulae (30 cases), external hemorrhage (one case), phlebitis (one case) and parotitis (one case).

An analysis of the 13 cases in which there were postoperative deaths re-

vealed that, preoperatively, three of the patients had partial intestinal obstruction, and five were recognized as poor risks because of debility or intercurrent disease. At operation, multiple internal openings or extensive defects in the bowel wall were found in nine cases. Extensive resections or plastic reconstructions were required in all but three cases. In one of these latter the patient was subjected to two extensive pelvic operations during a period of nine weeks, one was a severely debilitated patient suffering from ulcerative colitis, and the third died following closure of large and small bowel openings and removal of tuberculous pelvic organs. Postoperative shock occurred in five of the cases in which death occurred. General peritonitis was the cause of death in eight cases (associated with pneumonia in one case). Pelvic peritonitis was the cause in two cases (combined with pneumonia in one and with extensive ulcerative proctosigmoiditis in the other), shock and inanition in one case, bronchopneumonia in one case, and erysipelas in one case.

COMMENT—Evaluation of the results of any given form of operative treatment was difficult because of the number of variables. The highest morbidity and mortality (18.2 per cent) rates accompanied resections. Yet these operations were carried out in the most difficult cases, in which the patients often were afflicted with other disease processes. Healing of the fistula was obtained in 51.9 per cent of those who survived resection. It is obviously unfair to compare these results with those following extraperitoneal closure, in which satisfactory results were obtained in four of five cases. Simple cuetage was followed by healing in only six of 14 cases. Intraoperative closure, the most common procedure, was attended by a mortality rate of 10.6 per cent, and healing occurred in 64.3 per cent. The least satisfactory results followed the diversion operations, in most of which a second operation would have been required to effect a cure. Yet the safety of the procedure (no deaths in ten cases) warrants its use in certain cases, in a few of which healing will occur without further interference. The remaining operations were performed in too few cases to justify any conclusions, but, in general, it may be said that, although healing occasionally followed drainage of an abscess or the removal of diseased pelvic organs, results were not as a rule satisfactory when the internal opening was not closed.

We attempted to determine whether there was any difference in results following entry into the abdomen through the old incision or a new one, or following closure with or without drainage. We were unable to correlate results with any of these factors.

When the results were considered in relation to the cause of the fistulae, it was found that satisfactory results were obtained in about 60 per cent of the cases in which the fistula followed appendicitis or diverticulitis, and in the miscellaneous group. The least satisfactory results occurred in the tuberculous (31.3 per cent healed) and "malignant" (38.5 per cent healed) groups. Healing was obtained in 47.4 per cent of the patients whose fistulae followed pelvic operations, and in 53.8 per cent of the cases with regional enteritis. There were no deaths in the "malignant" group, chiefly because few extensive

procedures were carried out. The mortality was 4.8 per cent in the "appendicitis" group, 11.1 per cent in the "tuberculous" group, 13.3 per cent in the "regional enteritis" group, 13.6 per cent in the "pelvic" group, 16.7 per cent in the "diverticulitis" group, and 23.1 per cent in the miscellaneous group.

We were unable to correlate operative results with the duration of the fistula before operation.

SUMMARY

A review has been presented of 155 cases in which abnormal communications between the small or large bowel and the surface of the body existed. In 128 of these cases operation was performed, with a mortality rate of 10.2 per cent. Because of the risk and difficulty associated with operative interference, every opportunity should be provided to encourage spontaneous healing. The nature of the fistula and the reason for its persistence should be determined as accurately as possible before operation. There can be no standard method of operating upon fecal fistulae, each case presenting a distinct problem of variable complexity.

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THE LIVER GLYCOGEN AND LIPID CONCENTRATIONS FOLLOWING INTRAVENOUS GLUCOSE ADMINISTRATION AND DIET IN THE DOG* AND MAN† IN THE PRESENCE OF LIVER DAMAGE

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THE INTRAVENOUS METHOD of administering glucose to surgical patients has become nearly universal and is frequently employed even when there is no contraindication to the ingestion of food by mouth. This is especially true in the preoperative preparation of the patient with extensive hepatic disease. In fact, Soskin¹ has recently stated that there is in these patients a "physiologic basis for intravenous glucose therapy," and has suggested that, with the intravenous method, more glycogen can be laid down in the injured liver than when carbohydrate is given by mouth. The widespread use by clinicians of the intravenous method of administering glucose would appear to indicate acceptance of Soskin's hypothesis. Evidence which we have obtained from the dog and man under a variety of dietary conditions leads us to question the validity of this concept.

The physiologic basis of intravenous glucose therapy, in the presence of hepatic damage, has been given by Soskin as follows: "A greater hyperglycemia is necessary to suppress the supply of blood sugar and to favor the deposition of glycogen in an acutely damaged liver than in a normal liver, however, when the blood sugar is raised to a sufficiently high level the damaged liver does respond like the normal, and ceases to supply blood sugar. The benefit derived from this limitation in the activity of the liver may be regarded as equivalent to the favorable therapeutic results obtained by limiting the activity of other damaged tissue and organs in order to facilitate repair. The fact that many toxic substances are excreted as glucuronates suggests that excess storage of carbohydrate favors detoxication."

Most of the patients with biliary tract disease, now receiving intravenous glucose therapy, have a component of chronic hepatic injury which is of long-standing, and a lesser or greater degree of acute injury which is conditioned, as a rule, by infection or by an obstruction of the common bile duct, either from stone or malignancy. There is considerable difference of opinion as to just how much damage a simple obstruction of the common bile duct can produce when previous hepatitis did not exist.

It has been generally agreed that the glycogen content of the liver in the

* The work on the dog was aided by a grant from Merck and Company

† The work on man was aided by a grant from the United Fruit Co

presence of bile duct obstruction is reduced^{2, 3} While the liver, acutely damaged by a variety of hepatotoxic agents, rapidly loses glycogen, there are no data now available which conclusively prove that under conditions of an adequate diet, considerable amounts of glycogen cannot be laid down in a sub-acutely or chronically injured liver

It is now 27 years since Opie and Alford⁴ published their experiments, which indicated that a carbohydrate diet protected the liver from injury by chloroform Shortly thereafter Davis, Hall, and Whipple,⁵ and Graham⁶ confirmed these findings In 1924, Moise and Smith⁷ reported that the diets used by these investigators did not consist of purified foodstuffs and that they were inadequate for maintaining the weight of normal animals These latter investigators found that a protein diet was more efficacious than a carbohydrate diet in protecting the liver from the effects of chloroform

Clinicians have attempted to increase the glycogen content of the liver prior, and subsequent, to operation on the basis recently stated by Banks and Sears⁸ that "abundance of hepatic glycogen forms the basis of the protective and regenerative action of high carbohydrate diets in liver necrosis" Evidence obtained in this laboratory,⁹ and since confirmed by other investigators,¹⁰ seriously questions the frequently repeated statement that glycogen *per se* plays a direct rôle in the protection of the liver from injury by chloroform

We¹² have found that the addition of a sufficient amount of an adequate protein (casein) in the diet is the best method now available to reduce the degree and extent of the hepatic injury which follows the administration of certain hepatotoxic agents Protein has a very marked lipotropic action and the reduction in the concentration of liver lipid which follows the ingestion of protein reduces the amount of the fat soluble hepatotoxic agents which can be held in the liver More important, is our observation that certain proteins, or their split-products, offer direct protection against substances such as chloroform Miller, Ross, and Whipple¹¹ have recently published data obtained in the dog, which suggest that "methionine and to a less extent cystine given by mouth or by vein 24 to 55 hours before anesthesia give a remarkable and almost complete protection to the protein-depleted dog against chloroform poisoning" Experiments recently conducted in our laboratory on the rat, fail to confirm these observations, in that, in this animal, methionine provided only a minor degree of protection

Messinger and Hawkins¹³ have extended our observations for they have shown that a high protein dietary protects the liver from arsphenamine necrosis, and Smith¹⁴ has shown that such a diet protects the liver from selenium poisoning and sulfanilamide hepatitis

Notwithstanding such clear-cut data, most clinicians must still agree with Banks and Sears,⁸ for the intravenous injection of glucose still occupies an important place in the therapy of the patient with biliary tract disease, especially of a surgical character

In this communication, we wish to present evidence from the dog that, even if glycogen storage is useful in protecting the liver from injury, such stores

cannot be maintained over periods of time by intravenous glucose therapy in amounts comparable to those commonly used in man. The data from man are given merely to demonstrate that, even in the presence of extensive injury, glycogen can be deposited in the liver and low concentrations of liver lipid can be obtained. The liver specimens were removed from patients undergoing operations for biliary tract disease under spinal anesthesia. We have been able to obtain these sections without in any way affecting the course of convalescence. The data demonstrate a similar relationship to that we have reported for the dog.¹²

Methods—The dogs used in this study were growing mongrels, in a good general nutritional state, and weighing from 8 to 12 Kg, when the study was begun. Previous to operation they had been on a high fat diet for about two weeks. The diets and analytic methods have been described in previous papers.^{9, 12}

The glucose was administered intravenously slowly as a 5 per cent solution, either twice or three times daily. Liver sections were removed for study approximately eight to ten hours after the completion of the last injection. In the animals fed by mouth, either voluntarily or by forced feeding, the last food was given the dogs approximately 17 hours before removing a section of the liver for study. The diets used in man varied considerably, due to individual desires of the patient. In addition to various foodstuffs, which were weighed before and after feeding, the patients received, at frequent intervals, banana-skim-milk-shakes reinforced with "Casec." A large portion of the additional protein was provided as cottage cheese.

Results—Dogs which have been cholecystectomized, and whose common ducts have been ligated, so that no bile can flow into the intestine, rapidly lose their appetites. When such animals were offered food consisting of a mixture of table scraps or a synthetic diet, they ate from 25 to 125 Gm per day (Table I). Upon such diets, in the amount ingested, the liver glycogen concentration decreased and the liver lipid concentration increased.

TABLE I
VOLUNTARY FEEDING—NO INTRAVENOUS GLUCOSE

Dog No	Days	Initial Glycogen Gm %	Final Glycogen Gm %	Initial Fatty Acids Gm %	Final Fatty Acids Gm %	Dogs Ate Gm -Daily
141	8		0.2		11.8	50-60
123	8		0.3		49.2	25-50
142	14		0.52		13.5	50-80
85	7	3.14	2.90	15.7	20.9	75-105
21	7	1.80	1.79	18.2	27.2	55-125
22	7	2.15	1.75	14.3	17.4	60-110
826	7	0.63	0.83	37.73	22.80	30-60
828	7	3.02	1.09	9.17	17.17	25-60
Average		2.15	1.18	19.02	22.49	

When, to similar animals, fed on similar diets, a 5 per cent solution of glucose was administered intravenously in amounts of at least 50 cc per Kg

REPAIR OF LIVER DAMAGE

of body weight, the original mean glycogen concentration was maintained and the lipid concentration decreased by approximately 20 per cent (Table II)

TABLE II

VOLUNTARY FEEDING PLUS INTRAVENOUS GLUCOSE

Dog No	Days	Initial Glycogen	Final Glycogen	Initial Fatty Acids	Final Fatty Acids	Dogs Ate Gm -daily
		Gm %	Gm %	Gm %	Gm %	
53	14	3 1	2 8	11 5	14 8	30-60
54	14	4 4	3 7	9 4	11 3	30-60
27	10	2 4	3 9	52 2	44 4	30-60
122	5	0 91	2 34	25 45	13 30	55-155
223	5	0 82	2 62	19 10	14 98	55-180
257	5	1 78	2 60	17 25	26 10	80-125
226	5	2 09	1 82	22 10	14 28	50-75
12	7	1 44	1 41	15 3	14 3	30-50
647	7	2 23	2 23	21 6	13 25	50-100
539	7	3 69	2 06	32 20	12 44	25-100
641	7	1 66	1 55	55 80	47 00	35-50
Average		2 23	2 46	25 63	20 56	

In a third group of dogs appetite was stimulated by the administration of thiamin chloride, and desiccated bile was administered by mouth. These dogs ate from 60 to 405 Gm of the diet each day and, in addition, received 50 cc of a 5 per cent solution of glucose intravenously. In such dogs the mean increase in liver glycogen was 84 per cent, and the liver lipid decreased approximately 20 per cent (Table III)

TABLE III

GOOD APPETITE PLUS INTRAVENOUS GLUCOSE

Dog No	Days	Initial Glycogen	Final Glycogen	Initial Fatty Acids	Final Fatty Acids	Dogs Ate Gm -daily
		Gm %	Gm %	Gm %	Gm %	
81	12	1 03	6 1	40 8	15 7	80-230
86	14	2 20	3 80	28 0	15 2	80-190
88	11	2 50	3 90	28 0	14 9	80-130
104	14	2 50	6 30	16 0	13 9	80-255
105	14	2 60	7 10	16 7	28 2	80-205
22	10	1 6	6 3	22 7	9 2	85-130
24	10	2 1	5 4	49 0	14 6	105-130
48	14	4 9	8 2	13 9	7 7	230-400
107	12	3 1	7 6	26 6	16 3	80-405
648	7	3 05	3 04	27 4	11 5	75-200
675	7	1 32	3 84	24 4	17 2	90-255
534	7	2 36	3 96	15 55	16 3	150-185
642	7	1 9	3 4	12 42	9 21	100-205
438	7	2 27	3 2	57 7	34 2	150-200
304	7	2 73	4 58	21 20	9 40	85-180
310	7	4 07	4 20	17 40	11 68	85-130
305	7	2 36	1 08	19 65	16 25	65-130
303	7	2 94	3 42	14 25	9 25	80-135
309	7	3 39	4 34	25 65	19 28	80-180
Average		2 57	4 72	25 12	19 49	

When forced feeding was instituted the situation was even more striking. The dogs, whose data are given in Table IV, were fed with a carbohydrate-protein mixture consisting of 80 per cent of the calories as a carbohydrate, and 20 per cent of the calories as protein (casein). No glucose was given

intravenously, but the dogs received approximately 88 calories per Kg of body weight per day. The mean increase in the concentration of liver glycogen was 236 per cent, and the decrease in liver lipid 73 per cent.

TABLE IV
FORCED FEEDING—NO INTRAVENOUS GLUCOSE*

Dog No	Days	Initial Glycogen Gm %	Final Glycogen Gm %	Initial Fatty Acids Gm %	Final Fatty Acids Gm %
112	14		4.08		12.1
40	7	2.4	14.9	11.1	4.8
78	7	1.1	7.0	48.7	27.8
31	7	1.4	11.4	16.4	7.0
33	7	1.5	7.4	27.1	11.0
35	7	3.3	8.3	10.3	7.4
36	7	1.4	3.6	16.8	23.7
39	7	2.1	12.0	19.8	9.9
821	7	2.8	4.97	38.3	18.8
48	14	4.9	8.2	13.9	7.7
Average		2.3	7.77	22.5	13.0

* Eighty-eight calories per Kg per day

In contradistinction to data, such as these, are those obtained when similarly prepared dogs were given glucose intravenously, without any food by mouth (Table V). Such animals were given 50 cc of a 5 per cent solution of glucose per Kg of body weight, or more, during each 24 hours. In such animals, the glycogen concentration decreased by 50 per cent and the liver lipid concentration remained unchanged.

TABLE V
INTRAVENOUS GLUCOSE ONLY*

Dog No	Days	Initial Glycogen Gm %	Final Glycogen Gm %	Initial Fatty Acids Gm %	Final Fatty Acids Gm %
22	7	2.13	1.75	14.3	17.4
50	8	1.8	0.2	22.1	20.8
178	5	1.21	2.90	40.52	42.75
224	5	1.53	0.39	53.85	33.30
172	8	1.80	2.38	14.88	15.06
175	8	1.23	0.50	13.34	16.30
307	7	4.59	0.42	19.27	24.08
176	5	1.31	0.45	47.40	41.02
312	7	2.06	0.93	17.77	14.14
817	7	1.40	0.06	34.95	24.30
14	7	0.96	0.08	22.7	28.10
15	7	1.61	0.54	12.8	16.00
643	7	2.06	0.62	11.81	15.20
672	7	0.11	1.18	57.8	46.20
673	7	2.11	1.25	20.10	16.40
674	7	1.68	0.63	27.4	17.20
528	7	2.15	1.86	12.77	19.17
532	7	2.44	0.21	11.07	13.24
441	7	0.53	0.9	23.9	48.8
443	7	2.54	0.66	11.4	32.9
447	7	2.38	0.45	14.2	30.4
448	7	2.93	1.3	14.6	20.6
449	7	0.94	0.63	14.8	15.3
Average		1.78	0.88	23.21	24.29

* 50 cc of 5 per cent solution of glucose per Kg of body weight

In Table VI are given some data on the concentration of glycogen and lipid in the liver of man with biliary tract disease, at the time of celiotomy, under spinal anesthesia. They demonstrate that an adequate diet in man, for at least one week prior to operation, conditions the composition of the liver. In no instance have we found a high lipid concentration of the liver following what we have considered an adequate feeding period.

TABLE VI

						Immediate Operation (Within 3 days of Admission)			5 Days or More Preoperative Diet of 2500 Calories or More—20% P, 6% F					
Disease	Pre-hosp	Pre hosp				Liver	Fatty	Gly-				Liver	Fatty	Gly-
Duration	Diet	Appetite	Weight	Pt	Sex	Pathology	Acid %	cogen %	Pt	Sex	Pathology	Acid %	cogen %	
Chronic	Low fat	Mod- erate	Obese	Sh	F	Chronic hepatitis Marked fatty in- filtration	11.8	2.9	Br	F	Chronic hepatitis, with cirrhosis	2.9	3.4	
Common duct ob- struction	Low fat	Hearty	Obese	Tr	F	Chronic hepatitis Extensive fatty in- filtration	15.4	2.9	Sk	F	Chronic hepatitis, with cirrhosis	3.7	6.7	
Acute— 3 mos	Low fat	Mod- erate	Obese	Sc	M	Extensive chronic hepatitis, with fatty in- filtration	7.9	2.2	Sk	M	Chronic hepatitis, with cirrhosis	3.4	3.1	
Chronic— 2 yrs	Unre- stricted	Hearty	Obese	Bu	F	Chronic hepatitis, with very extensive fatty in- filtration	11.0	3.1	Ki	F	Chronic hepatitis, with mild cirrhosis	4.1	3.2	

Discussion—The data, presented in this communication, strongly support the concept that the amount of glycogen present in the liver, at any given period, depends to a large extent upon the amount of carbohydrate, or carbohydrate-forming substances available to the animal or patient. If, as we doubt, any great virtue, in itself, lies in obtaining a high concentration of hepatic glycogen, this can be obtained only by supplying a sufficient number of calories during the period of therapy.

The increasing tendency to place more and more emphasis on the greater value of intravenously injected glucose is fraught with the gravest of danger, for, as this is done, less emphasis is placed upon the administration of food-stuffs by mouth. It can be stated, with considerable confidence, that unless more calories are provided than are necessary to meet the energy requirements of the animal, or man, by diet or intravenous therapy, glycogen or protein will not be laid down in the liver.

It is impossible to supply sufficient calories for the energy requirements of man by any method of intravenous therapy now available. The usual program in this country is to administer to these patients 3,000 cc. of a 5 per cent solution of glucose every 24 hours. This provides but 600 calories from an

exogenous source, less than one-third of those needed by these patients for simple energy requirements. Even if the concentration is doubled, and this cannot be done for long periods, because thrombosis of veins occurs more readily and the renal spilling of glucose is encouraged, the caloric intake is still below that necessary to prevent extensive tissue destruction. Under such circumstances, foodstuffs cannot be more than temporarily stored in the liver for they must again be mobilized rapidly to meet the metabolic demands of the body.

A program of this type will constantly result in a demand upon the patient's tissues in order that the energy requirements of the patient be met. Such a circumstance regularly occurs in most hospitals, and the loss of weight which nearly every one of these patients undergoes is an expression of the extent to which food intake has failed to meet the energy requirements.

If the premises advanced by Goldschmidt, Vars, and Ravdin⁹ are correct, the value of adequate protein in diet in the prevention of liver injury should rapidly be recognized. Not only does adequate protein in the diet protect the liver from a variety of hepatotoxic agents through some inherent properties of the foodstuff itself, but as Johnson, Ravdin, Vars, and Zintel¹² have shown, protein is more efficient in the presence of ductal obstruction in reducing the concentration of hepatic lipid than is carbohydrate. Finally, if repair is to be facilitated, protein must be available, for regeneration cannot readily take place on carbohydrate alone, especially when the protein stores of the body have been depleted by undernutrition. When repair does take place, following intravenous glucose therapy, the tissues of the body must supply the protein necessary for cellular regeneration.

The data of Banks and Sears⁸ suggest that when equivalent amounts of glucose are given by mouth and intravenously, glucose "was slightly more efficacious by vein than by mouth in raising the glycogen content of the liver in dogs with obstructive jaundice." They pointed out, however, that "a caloric intake consisting entirely of dextrose and adequate to meet the daily energy requirements of the dog, was less productive of hepatic glycogen than a general diet with supplementary dextrose therapy."

It is our belief that adequate amounts of glucose, administered just prior to operation, may, in part, be deposited in the liver, but that such glucose will neither protect the liver from injury nor facilitate repair. Only by a fuller knowledge of the energy requirements of man, of the foodstuffs essential to meet these, and of the part which they may play in conditioning injury and promoting repair, can we prepare patients with hepatic injury satisfactorily for operation and convalescence.

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TORSION OF THE GREAT OMENTUM*

REPORT OF TWO CASES

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TORSION, or twisting of the omentum on its long axis, has been recognized for a long time as a rare clinical entity although the diagnosis of this condition has seldom been made before operation

Aimes¹ credited Marchette with the report of the first case of torsion of the omentum, in 1851, Oberst,¹⁰ however, was the first to record this condition, in 1882 Demons⁶ reported another case, in 1893 In each of these two cases, a right inguinal hernia acted as a predisposing factor Eitel⁹ (1899) was the first to report a case of omental torsion unassociated with a hernia Since that time many reports have appeared in the literature, notably that by Corner and Pinches,⁵ which collated 54 cases up to 1905 (including three of their own), and that by Morris,¹⁷ in 1932, in which 161 authentic cases of torsion of the omentum, from 1905 to 1930, were compiled, and three personal cases were added His own series and that of Corner and Pinches permitted Morris to make careful analysis of this condition The results of this study show that, while torsion of the omentum may occur at any age, it occurs most frequently between the ages of 30 and 50 (83 cases, 52.5 per cent), that males are more commonly affected than females in a ratio of two to one, and that the condition is associated with inguinal hernia (89 per cent in Corner and Pinches's series, and 50.3 per cent in Morris's) The analysis of Morris's cases further emphasized the facts that the herniae were of the right inguinal variety, were scrotal in type, of long duration, easily reducible, and that they almost invariably contained omentum

McWhorter,¹⁶ in 1928, reported 26 cases (including two of his own) of torsion of the omentum of the so-called idiopathic type, that is, cases arising within the peritoneal cavity, not associated with hernia, in which the causative factors were obscure

The series reported here consists of the 16 cases reported in sufficient detail for analysis, since 1932, with two additional cases not previously reported (Fair and Bachman)

The classification offered by Morris is simple, though comprehensive, and facilitates the study and understanding of this condition

(A) Complete Torsion

(1) Acute torsion with hernia

(a) Hernial

(b) Hernial and abdominal (combined)

- (2) Acute torsion without hernia (purely abdominal)
 - (a) Primary or idiopathic (unipolar)
 - (b) Secondary (unipolar and bipolar)
- (B) Incomplete Torsion
 - (1) With hernia
 - (a) Hernial
 - (b) Combined
 - (2) Without hernia
 - (a) Primary
 - (b) Secondary

Fair and Bachman ¹¹	7 cases	Lucca ¹⁵	2 cases
Beigquist ³	2 cases	Baisky and Schwartz ²	2 cases
Poling ²¹	1 case	D'Eliico ¹⁰	2 cases
Total 16			

Under this classification, it is understood that the terms "complete" and "incomplete" refer to the degree of torsion, complete torsion signifying cases in which the twisting of the omentum on its axis has caused sufficient interference in circulation to produce evidence of strangulation in the affected part of the omentum

It is claimed that incomplete torsion may be of the "recurring" type, and that it is a definite clinical entity which can be recognized as such. Patients suffering from recurring abdominal pain may have temporary twists of the omentum. The "omental ball" and the omental fibrotic thickenings occasionally found, result from these recurring attacks of incomplete torsion of the omentum. The chronic changes occasionally found in the omentum in acute omental torsions seem to substantiate the occurrence of the recurring type of incomplete torsion. The case reported by Baisky and Schwartz,² for example, points strongly toward this possibility. A child, five years of age, had a history of frequent "colic" and, at operation for acute torsion, the omentum showed definite fibrotic changes.

Most cases of torsion are associated with hernia, a certain number, however, are caused by inflammatory foci within the abdominal cavity, which produce an inflammation in the neighboring omentum by contiguity. This may be true in cases of mild or subsiding appendicitis or cholecystitis in which the original focus subsides, but the changes induced in the omentum persist. The presence of a hernia containing omentum may eventually produce changes in the latter by means of constrictions or twisting of the pedicle in the neck of the hernia causing thickenings in the portion of the omentum within the sac. Thus a pathologic locus in the omentum is instituted.

Etiologic factors of torsion have also been traced by some (Robinson²²), to the function ascribed to the omentum, that of "the policeman of the belly." It has been assumed by many that the omentum plugs up a perforation in a hollow viscus, and wraps itself around or attaches itself to an inflammatory focus in an attempt to wall-off the rest of the peritoneal cavity. This view

was flatly contradicted by the studies of Draper and Johnson,^{7,8} whose critical review of the literature and of experiments conducted to clear up these points led them to believe that the only function of the omentum is bactericidal and absorptive, and that it possesses no automotile or ameboid characteristics of negative or positive chemotaxis

According to Draper and Johnson, only in the quadruped has the omentum any definite function. It serves as a fat pad between the viscera and the hard abdominal muscles, and as a storage place for fat during the lush feeding period. In man, it is a vestigial organ, variable in size and shape. Some persons have an omentum so small that it is hard to conceive its possessing any function at all. Any apparent protective powers displayed by the omentum are purely accidental in nature. The author is inclined to accept this view for, were the omentum to possess a function, it would gain a more definite place in pathology. Pathologic conditions of the omentum are comparatively rare and are associated in the great majority of cases with inguinal hernia or some other intra-abdominal pathologic change.

The more acceptable predisposing causes, in the idiopathic type of torsion, are anatomic and physiologic in nature. The omentum is variable in size and deposition of fat. It may be in the form of an apron, with irregular deposits of fat, or may be composed of several fat-laden strings. The right side of this structure is usually lower than the left and may reach into the pelvis. There may be accessory omental lobules of moderate size attached to the border of the main omentum.

In addition to being the seat of more frequent pathologic processes, the lower right quadrant is also the place of greater physiologic activity, intestinal peristalsis and changes in intra-abdominal pressure tend toward the right side. This seems to be borne out by the significant findings of Bernstein⁴ "That, in spite of ovarian tumors occurring with almost equal frequency on both sides, yet torsion of these is twice as frequent on the right as on the left side." This impression is further strengthened by the fact that almost all cases of torsion are found in the right half of the abdomen, especially in the lower right quadrant.

Payr²⁰ offered another explanation for the occurrence of the abdominal type of torsion on the basis of the fact that the omental veins are more tortuous and more easily compressed than the arteries. According to him, engorgement of the tortuous veins may cause a partial or complete torsion of the omentum. Other factors then enter—the degree of twist, interference with the circulation beyond it, the anatomy of the omentum, or possibly a pathologic condition of the omentum itself. Recovery may ensue or the process may go on to complete atrophy or gangrene. Cases have been reported in which the omental tumor thus produced, became parasitic through its attachment to other viscera.¹³

Contributory factors mentioned in the literature, such as trauma to the abdominal wall, coughing, efforts at lifting, bicycle racing, hard labor, inges-

tion of heavy meals, violent purgation, or the taxis of hernia, probably act to complete an existing process of incomplete torsion. The conclusion may reasonably be reached that, in the greatest percentage of cases associated with hernia, the easily reducible portion of the omentum within a hernial sac undergoes inflammatory changes, the pedicle is gradually thinned-out and the repeated traveling of the herniated portion of the omentum in and out of the sac leads to torsion, incomplete until some sudden physical effort on the part of the patient influences factors within the abdomen to produce complete acute torsion. In two-thirds of the cases, the presence of a hernia is the predisposing cause.

According to Morris, the right side is more often affected because of these two factors: (1) The right side of the abdomen is the seat of more frequent pathologic processes, cholecystitis, gastric and duodenal ulcers, and especially appendicitis. (2) The omentum, lying in proximity to these, becomes secondarily involved and very often fixed to an inflammatory process. Thus an inflammatory condition favoring torsion is established in the omentum. If a point of fixation is produced, bipolar torsion may result.

It is more difficult to explain the idiopathic variety of torsion in which no discernible intra-abdominal conditions predisposing to torsion are found. The fact that torsion of the omentum has occurred in well-developed obese persons would lead one to suspect that the omentum was loaded with fat, the edge of the apron being more heavily laden than the rest, thus serving as a weight on a plumb-line, with the constant peristaltic action of the intestines favoring torsion. The rest of the mechanism has been discussed above. It is quite possible that venous tortuosity, as noted by Payr, is instrumental in initiating the process in these stout persons, causing mechanical changes in the omentum beyond a point of free lymphatic and venous circulation. One questions this mechanism as being the major cause in idiopathic torsion, for, were this factor alone operative, many more cases of intra-abdominal torsion would be recorded instead of 11 per cent in Corner and Pinches's series, 47.8 per cent in Morris's, and 87.8 per cent in this series of 18 cases. In the absence of function of the omentum, a likely explanation of idiopathic torsion is offered in the statement credited by Fuller¹² to Reidel, namely, that no torsion would occur were the omentum free from pathologic change. How this pathologic change in the omentum is produced still needs clarification. Perhaps the cause lies in internal hernial openings operating to produce an "omental ball," or changes in the omentum, produced by the intra-abdominal pathologic processes discussed above. These leave no gross evidence in the organ itself but give rise to sufficient alteration in the omentum to serve as the initial point for torsion under favorable circumstances.

A careful analysis of the 11 cases of the purely intra-abdominal type in this series, fails to reveal any explanation for the condition. It is true that in none of these were observations made seeking the cause. Morris's study also failed to bring forth any more definite explanation for this type of tor-

sion The immediate causes for the torsion were ascribed to various physical efforts (dancing, lifting a heavy weight, *etc*) Only two patients in this series gave a history of any possible antecedent cause, in one the torsion followed the ingestion of a hearty meal, in the other, it occurred while the patient was driving an automobile (Farr's case) The etiology of idiopathic torsion of the omentum is still obscure in spite of our greater clinical knowledge and better understanding of this condition

REPORT OF TWO CASES

Case 1 *—C S, a waiter, age 37, was admitted to the hospital, August 8, 1932, with the diagnosis of incarcerated hernia The patient had had a right inguinal, reducible, scrotal hernia for 14 years The hernia became irreducible on August 24, 1932 (four days prior to admission), and the patient developed symptoms of urgency and frequency of urination, soreness along Poupart's ligament, and swelling and induration of the right testicle The patient had not had a bowel movement for the four days prior to admission but showed no signs or symptoms of intestinal obstruction

Physical Examination—The patient was a well-developed, well-nourished male There was no tenderness or rigidity of the abdomen, and no abdominal masses were noted except a tender bulge, about 5 cm from the right external inguinal ring to a point above Poupart's ligament The right scrotum was filled with a sensitive mass, 3 cm in diameter The testicle was felt as a separate mass and was three times larger than the left No varicocele or hydrocele was noted on either side No diagnosis was made prior to operation

Operation—September 1, 1932 The sac was found to contain omentum only The abdominal portion of the omentum was found to be gangrenous and twisted six times on its axis The omentum was removed as high as the transverse colon Following the operation, the patient developed paralytic ileus and bronchopneumonia, and expired September 5, 1932

COMMENT—This case comes under the classification of acute torsion, hernial and abdominal, bipolar

Case 2—J G, a carpenter, age 36, was seen, December 18, 1936, because of an acute intra-abdominal condition He had always been well and had had no previous operations Three years previously, the patient had developed a right, incomplete inguinal hernia He had been told at that time that he also had a large left inguinal ring He had worn a truss for the three years and had no reappearance of the "lump" at the right external ring for the past two years, in spite of the fact that he had left off the truss on several occasions, for days at a time, while engaged in heavy work as a carpenter on construction jobs

On December 16, 1936, after a heavy meal of corned beef and cabbage, the patient was awakened in the middle of the night by cramps in the upper abdominal region He vomited a slight amount once, but the pain was not relieved The patient slept comfortably the rest of the night but had chilly sensations in the morning The upper abdominal pain became steady and dull in character Attempts at eating resulted in an increase in the pain, without vomiting or nausea In spite of the persistence of pain he had a full meal that evening and a hearty breakfast the next morning During the next two days the pain recurred but was somewhat less when the patient lay down

* This case was the only instance of torsion of the omentum which was recorded at the San Francisco Hospital, University of California Service, between the years 1919 and 1937 This is reported through the courtesy of Dr Harold Brunn, Chief of the University of California Surgical Service at the San Francisco Hospital

Sleep was disturbed during this period. On the third day, the pain shifted from the upper abdomen to the right lower quadrant, and all the tenderness and soreness in the upper abdomen disappeared. Sodium bicarbonate, by mouth, gave him no relief. An enema made him feel worse. At no time did he have any belching, distention or local tenderness.

Physical Examination—The patient was a very robust, well-developed male, who looked chronically ill. The heart and lungs were normal. There was moderate rigidity of the entire right side of the abdomen, with tenderness to the right of the umbilicus and some slight rebound tenderness in the lower quadrant. No masses were felt in the abdomen or on rectal examination. The red cell count was normal. The white cell count was 6,500, with 87 per cent polymorphonuclear cells.

An exploratory celiotomy, with the possibility of acute appendicitis in mind, but with no diagnosis having been made, was performed December 19, 1936. The age of the patient, the blood count, and the entire course of the attack during the three days prior to the operation did not conform to any of clinical entities considered. Torsion of the omentum was not even thought of.

Operation—A slightly injected appendix was found. The omentum consisted of flat semigangrenous tissue, two by three inches in size, suspended by a pedicle which was twisted on its axis five times. There was no free fluid. The mass was removed. Further exploration of the peritoneal cavity revealed no apparent cause for the torsion. The patient made an uneventful recovery.

COMMENT—In spite of the history of hernia of the right side, we felt that it did not cause the torsion. The hernia was not of the complete reducible type. There had been no evidence of it for the two years prior to the occurrence of torsion. Yet the possibility that the hernia initiated the pathologic process in the omentum could not be ignored.

A comparison of the findings in three series of cases (Corner and Pinches, 53 cases, Morris, 164 cases, and the present study of 18 cases) is of interest. Our series bears out Morris's findings (in his own series and that of Corner and Pinches's) that torsion of the omentum occurs twice as frequently in men as it does in women. Inguinal hernia as the main etiologic factor, however, has lost its importance. It was considered to be the cause of torsion in 89 per cent of the cases reviewed by Corner and Pinches, and in 50.3 per cent of Morris's series, but in only 22.2 per cent of the present series. With more frequent and earlier attention to hernia, this type of torsion has diminished. The age at which torsion occurs has not changed materially. A history of previous symptoms suggesting the possibility of recurring torsion was present in 16 cases in the first series, 27 cases in the second, and in two in the present study. None was more than suggestive, but a history of sudden severe muscular effort, a sharp blow on the abdomen, an abrupt movement involving changes in intra-abdominal pressure, or a hearty meal, was present in a sufficient number of cases to point to these as exciting causes in torsion. The sudden onset of pain in the right side of the abdomen was a constant finding.

The differential diagnosis of acute torsion of the omentum, either hernial or idiopathic, is difficult and has seldom been made before operation. On the other hand, almost every variety of acute intra-abdominal condition has been mistaken for torsion—intestinal obstruction, tuberculosis of the cecum, torsion of the spermatic cord, perforated peptic ulcer, etc. There are, perhaps, more

suggestive diagnostic features in the hernial type than in the abdominal. According to Morris, the sequence of events in torsion associated with hernia is somewhat as follows. The patient, an obese man, of about middle age, who has had a reducible, complete, right inguinal hernia for a long time, suddenly—usually after severe muscular strain—finds the hernia irreducible. Pain and swelling appear in the hernial site. Nausea and vomiting are present, and an increase in pain develops. The pain gradually ascends into the abdomen and becomes localized in the right lower quadrant, or at the right side of the umbilicus. The patient's condition becomes progressively worse, abdominal rigidity and tenderness appear and a movable abdominal mass can be palpated. There is a slight elevation of temperature, and leukocytosis may be evident. The usual diagnosis is strangulated hernia, but the possibility of acute appendicitis cannot be ignored. At operation, gangrenous omentum is usually found in the hernial sac.

The abdominal, or idiopathic type of torsion, is even more baffling. Of the six abdominal cases reported by Corner and Pinches, five were diagnosed as acute appendicitis and one as suppurative omental hydatid cyst. These authors credit Lucas-Champonnière with the first reports of two cases correctly diagnosed before operation (1900, 1901). McWhorter, in a collection of 26 cases of the abdominal type, recorded no correct diagnosis, except Lucas-Champonnière's. Morris recorded only three correct diagnoses in cases of the idiopathic variety. In none of the present series was the correct diagnosis made before operation.

The simulation of acute appendicitis and acute cholecystitis, by torsion, is such that it is most often mistaken for one or the other of these conditions (over 75 per cent of cases of torsion were so diagnosed). The diagnosis of acute appendicitis was made twice as often as that of acute cholecystitis. This was especially true in the idiopathic type. The attempt by Smythe, Jeffries, and Mullen²³ to differentiate between torsion and acute appendicitis according to individual symptoms is not helpful. As pointed out by Morris, his largest series did not conform to the clinical picture of torsion as obtained by the foregoing authors. Morris, further, makes the point that no clinical symptom in appendicitis or torsion is specific. The present study tends to substantiate the opinion that it is almost impossible to differentiate torsion from acute appendicitis by means of a consideration of the rise in temperature, pulse rate, the blood count, or the presence of nausea and vomiting. A presumptive diagnosis of torsion may be made, however, when a robust man, in the third, fourth, or fifth decade of life, is suddenly seized with abdominal pain after a severe muscular effort or strain, and when, upon examination, a mobile mass is suspected or definitely felt to the right of the umbilicus. Mullen and Smythe attest the early appearance of such a mass, its mobility, its situation toward the midline, and the percussion of an area of resonance toward its one side. The fact was also emphasized that the symptoms in acute torsion are not so severe or so prostrating as they are in acute appendicitis. This explains the

longer delay in seeking medical attention. In the present series, the average interval between the onset of symptoms and surgery was two days.

One patient had had symptoms for two months. A diagnosis of acute cholecystitis was made but celiotomy disclosed a gangrenous omentum. Similar findings were present in a case of only a few hours' duration. The pathologic changes found at operation, such as hemorrhage or gangrene, depend on the degree of strangulation of the omentum. A serous or bloody exudate is present, and the presence of fluid may sometimes be elicited before operation. The finding of fibrotic changes in the involved portion of the omentum is indicative of a recurrent type. The number of twists (from three to 11) found in some of these cases is suggestive of a slow process of torsion, until the circulation of the omentum is compromised, when all the reflex phenomena express themselves as the symptoms described above.

Both Corner and Pinches, and Morris, stressed the possibility of a combined form of torsion in those cases in which the neck of the sac shows no constriction and the twisting extends into the abdomen. A hemiocoeliotomy is necessary in these.

The various hypotheses as to the rôle played by anatomy and physiology of the omentum in the pathogenesis of torsion has already been considered. Very little actual information is recorded in the reports of cases of the abdominal type of torsion which might help in the understanding of the pathogenesis of this condition. Yet, a thorough exploration in these cases would probably discover possible causes for torsion. A plea is made for obtaining more complete data in the idiopathic type of torsion, noting especially the following:

- (1) Hernial openings, external or internal, which might operate in the production of pathologic changes in the omentum.
- (2) Inflammatory foci, acute, chronic or healed, which might explain initial changes in the omentum.
- (3) Peculiarities in the anatomy of the omentum which might favor torsion.
- (4) Other abnormalities which might serve to explain the occurrence of torsion.

Surgery is the only treatment. Recovery is the rule unless complications set in.

SUMMARY

(1) Sixteen cases of torsion are reviewed, and two additional cases are reported.

(2) An analysis of the hitherto reported cases is made.

(3) Emphasis is laid upon the increasing number of the idiopathic variety of torsion. Attention is called to the more common occurrence of torsion in the right half of the abdomen.

(4) Diagnostic points are stressed.

(5) A plea is made for more accurate observation and study of these cases.

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RIGHT PARADUODENAL HERNIA

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A PARADUODENAL HERNIA is a condition in which most of all the small intestine is incarcerated behind the folds of the mesocolon, making its entrance in the area of the duodenojejunal junction. This type of hernia comes under the classification of an internal or retroperitoneal hernia and comprises 53 per cent of all the internal herniae found. Two types occur (1) Right paraduodenal hernia, and (2) left paraduodenal hernia. The latter is the more common, the ratio being about three to one. There have been 47 cases of right paraduodenal hernia reported, operation having been performed in 28 instances, with 15 recoveries.

The following conditions are usually found in a right paraduodenal hernia (Moynihan¹⁹) (1) The sac occupies the right half of the abdominal cavity, lying behind the ascending and transverse mesocolon, (2) the orifice is situated to the left of the sac, and (3) in the anterior margin of the sac, there lies either the superior mesenteric artery or a continuation of it, the ileocolic artery.

The case herewith reported is of interest because of its rarity and the unusual anatomic derangement associated with the hernia.

Case Report—A female, age 49, was admitted to the hospital, September 17, 1939, complaining of vomiting, abdominal pain, and distention. The patient did not speak English and her history was obtained with difficulty through a Spanish interpreter. She stated that since the age of one year she had had "stomach trouble" consisting of attacks of abdominal pain with distention and occasional vomiting and diarrhea. These attacks were irregular but occurred at least once every three months. In 1929, she was told by a physician that she had an ulcer of the stomach. She followed a modified Sippy diet for a short time without improvement. She had observed that the severity and duration of the paroxysms were diminished on lying down. Every attack had been precipitated while she was on her feet. Food idiosyncrasies apparently had nothing to do with the onset of her periods of illness as she had been incapacitated at times when she had not eaten. September 1, 1939, the patient began having pain in the lower abdomen which soon radiated to her epigastrium and was accompanied by vomiting. This lasted six hours and was relieved following an enema. A diarrhea developed following this episode but rapidly subsided. The stools had a normal color. The patient had never menstruated, had been married 25 years, and had never been pregnant. She stated that she had had heart trouble, but the history of this was vague.

Three days before admission, September 14, 1939, the patient developed pain in her lower abdomen following the ingestion of some corn. The pain soon became generalized, and vomiting and distention of the abdomen became evident. Daily enemas did not produce fecal material and the symptoms persisted.

The relevant physical findings were obvious signs of dehydration, an oral temperature of 100° F, a blood pressure of 170/100, cardiac enlargement to the left, a distended and tympanic abdomen, with exaggerated borborygmi, which could be auscultated over the entire abdomen, and generalized tenderness with rebound tenderness. All the labora-

tory findings were normal (blood count, Kline, and uranalysis) *Clinical Diagnosis*
Intestinal obstruction

She was given intravenous fluids of glucose and normal saline, a Miller-Abbott tube was started, and a barium enema was given. The roentgenologic diagnosis, made by Dr. E. Hayden, was obstruction in the jejunum or proximal ileum, constriction of the midtransverse and sigmoid colon (Fig 1), and apical tuberculosis was found by fluoroscopy. The patient's symptoms were not improved after eight hours of treatment, and it was thought advisable to explore the abdomen, as strangulation of the intestine was feared.

Operation—Under cyclopropane anesthesia, a low midline incision was made. On opening the peritoneal cavity a confusing anomaly of the anatomy was found. No small intestine was to be seen. The transverse colon lay in the pelvis, attached by firm adhesions to the descending colon, the sigmoid, the peritoneum overlying the bladder and to the pelvic viscera. The adhesions between the transverse colon and the vesico-uterine peritoneum were cut to allow exploration of the pelvis. It was found that an infantile genital system existed. Superior to the transverse colon a mass could be palpated but not visualized. The incision was extended upward and around the umbilicus. At this point a mass could be seen which filled the upper portion of the abdomen. Intestines were seen to be enclosed in the tumor and it was recognized that a paraduodenal hernia was present. An attempt was made to find the opening leading into the sac but none was found. The hernial sac wall, consisting of the gastrocolic ligament and the mesentery of the ascending colon, was opened through an avascular area. The intestines were reduced through this opening, and it was found that the entire jejunum and greater portion of the ileum were contained in the hernial mass. There were several areas of purplish discoloration present in the bowel wall which recovered their normal color after reduction. By manually exploring the hernial cavity, the orifice was found to the left of the sac. This could be visualized only after adhesions between the transverse and descending colon were freed and the ptosed transverse colon retracted medially. The orifice was fully three inches in length, and the superior mesenteric artery traversed its anterior margin. The first portion of the jejunum entered the upper angle of the orifice into the hernial cavity and the distal end of the ileum emerged from the lower portion. By traction the intestine which had been incarcerated was pulled through the hernial orifice. Due to the length of the gastrocolic ligament, and the adhesions between the transverse colon and lower abdominal viscera, the position of the small intestines was still abnormal but ample room was afforded for them posterior to the gastrocolic ligament and superior to the transverse colon (Fig 2). The hernial orifice was sutured with interrupted sutures of silk and the abdomen was closed in layers.

The patient's condition was good at the end of this procedure and continued so until the second postoperative day when signs of cardiac decompensation were observed. Digitalis was started followed by rapid improvement, after which the patient's recovery was uneventful. She was discharged from the hospital October 8, 1939, and has had no further signs of obstruction and no abdominal pain.

By reviewing the embryology of the intestine, the formation of a paraduodenal hernia can be better understood. The primitive gut arises in the human embryo when the entoderm is folded into a simple tube. This opens into the yolk stalk and is supported on the dorsal wall by the mesentery. During the fifth week the attachment of the yolk stalk disappears, the anlage of the cecum is formed, and there is a rapid elongation of the small intestine, which causes it to be thrown into a loop opposite the point of attachment of the yolk stalk. This loop rotates counterclockwise, and as a result the cecal

portion of the intestine lies to the left and the small intestine to the right (Plate I—Fig 1) The small intestine continues to lengthen so rapidly that it can no longer be accommodated in the abdominal cavity, and, at seven weeks, it herniates into the umbilical coelom (Plate I—Fig 2) The hind gut (major portion of the large intestine) is retained in the abdomen In embryos of ten weeks the intestine returns into the abdominal cavity and the coelum is obliterated The proximal coils of the small intestine are reduced first behind the superior mesenteric artery while the cecum returns last As a result there occurs a counter-clockwise rotation of 270° about the axis of the artery, throwing the duodenum behind and the transverse colon in front of the artery Following the rotation the cecum lies to the right occupying a position immediately below the liver with the small intestines lying medially (Plate I—Fig 3) In three- to six-months' fetuses the lengthening colon causes the cecum and cephalic end of the colon to descend toward the pelvis, and the ascending colon is thus established (Plate I—Fig 4)



FIG 1—Roentgenogram of abdomen following barium enema showing dilated loops of small intestine and ptosis of transverse colon The diagnosis of paraduodenal hernia could not be made from this film

With the elongation of the intestines, the mesentery grows correspondingly and is carried with the intestine in its rotation The superior mesenteric artery serves as the axis for the rotation The axis is accentuated as the cecum descends and the mesentery is spread out like a funnel During the fourth month the descending and ascending colons and their mesenteries fuse with the dorsal peritoneum (Plate I—Fig 4)

The process just described is the normal development of the gut Paraduodenal herniae are the result of an abnormal rotation of the intestine

The formation of right paraduodenal herniae has been excellently described by Andrews,¹ and will be briefly reviewed During the tenth week, when the intestine leaves the umbilical coelom, if an incomplete rotation of the cecum is present, this portion of the gut would lie inferior to the small intestines (Plate I—Fig 5) As it grows to the right it would scoop up the small intestines in its mesentery (Plate I—Fig 6), and when fusion occurs, during the fourth month (Plate I—Fig 7), the small intestines would be imprisoned posterior to the mesentery

The first paraduodenal hernia to be diagnosed preoperatively was reported in 1930, by Taylor²³ Only two such diagnoses have been made, and these were made roentgenologically A large number of patients with these herniae do not have symptoms and the anomaly is found at necropsy In other cases

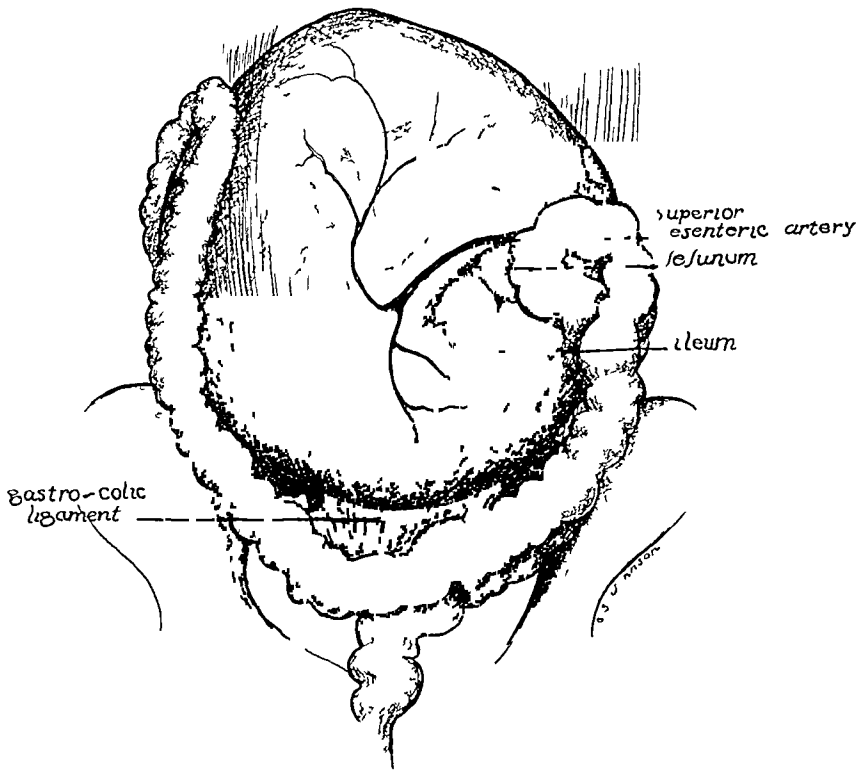


FIG. 2.—Drawing showing the anatomic relations found at operation. The paraduodenal hernia's anterior wall consisted of the mesentery of the transverse colon and gastrocolic ligament. The transverse colon lay inferior to the sac, and a portion of the colon overlapped the hernial orifice.

there are indefinite symptoms of colic-like abdominal discomfort which may be transient and with or without vomiting. The diagnosis of gallbladder disease, "dyspepsia," pyloric spasm, *etc.*, may be made. Again, there may be a sudden onset of symptoms indicating an acute intestinal obstruction. Bile is frequently present in the vomitus, but fecal vomiting is uncommon due to the usually high site of the obstruction. Moynihan¹⁹ and Garber¹¹ both consider the chief diagnostic signs to be repeated attacks of abdominal colic, abdominal tenderness, with distention relieved by the passing of flatus, visible peristalsis, and a palpable, tympanitic, elastic mass in the abdomen. Scheele²¹ claims that roentgenograms taken following a barium meal show retention in the stomach and duodenum, with a bow-shaped closing off of the upper intestinal shadow. A barium meal is contraindicated in cases with acute symptoms. Eaker⁸ states that the clumped appearance of the intestinal coils, shown in a "flat" roentgenogram, as if they were contained in a sac, is a characteristic sign of paraduodenal hernia. In large herniae, such as the

RIGHT PARADUODENAL HERNIA

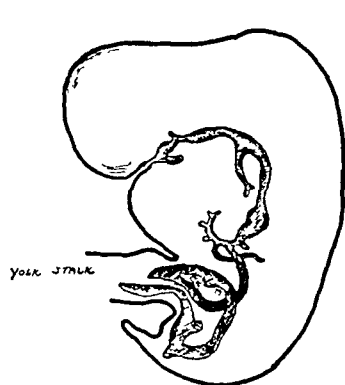


FIGURE 1

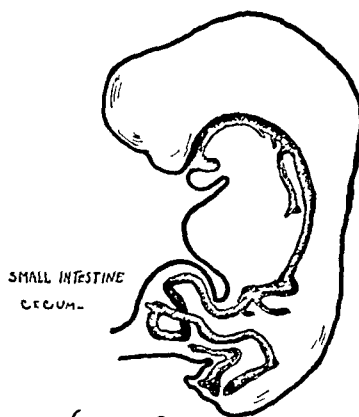


FIGURE 2

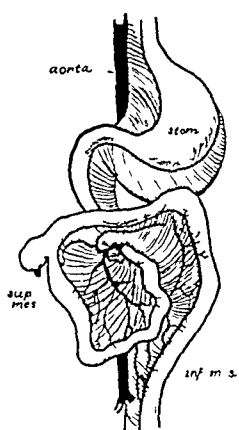


FIGURE 3

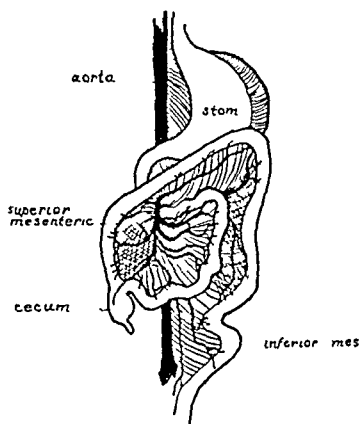


FIGURE 4

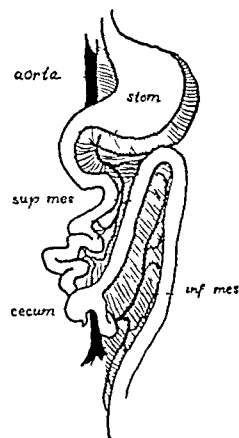


FIGURE 5

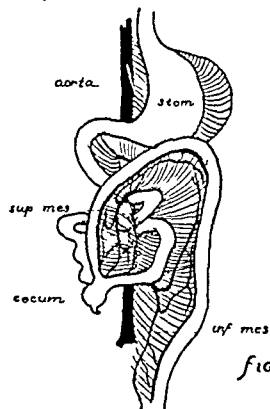


FIGURE 6

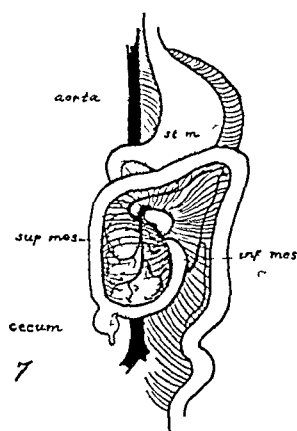


FIGURE 7

PLATE I

FIG 1 —Diagrammatic fifth week embryo showing counterclockwise rotation of the intestinal loop

FIG 2 —Seventh week embryo with herniation of the small intestine into the umbilical coelom

FIG 3 —Position of large and small intestine following normal rotation in a ten week embryo

FIG 4 —Normal rotation complete, with cecum in right lower aspect of the abdominal cavity. Shaded areas represent areas of fusion between the mesenteries and the posterior peritoneum

FIGS 5 and 6 —Illustrating the relative positions of the large and small intestine when incomplete rotation occurs. The cecum lies inferior to the small intestine and as it grows to the right the small intestine is caught and enclosed in its mesentery. (After Andrews¹)

FIG 7 —In the fourth month the fusion of the mesentery and peritoneum has incarcerated the small intestine and completed the right paraduodenal hernia. Note that all conditions of the right paraduodenal hernia are reproduced, the sac and its contents occupy the right portion of the abdomen, the orifice is to the left of the sac, and the superior mesenteric artery lies in the anterior margin of the sac

one described above, there is no roentgenographic evidence that the intestines are enclosed within a limited space

The treatment advisable for this condition depends largely on the symptoms and findings present. Those herniae found in the course of the abdominal surgery should be reduced and the neck of the sac closed. When signs of an intestinal obstruction are present, the treatment should be the same as in any other case of obstruction. In cases with evidence of strangulation, surgery should not be delayed. If the hernial orifice cannot be located, an avascular area on the sac wall can be opened and the cavity explored manually. It was only by this method that the opening was found in the above described case. Caution must be exercised to protect the vital blood vessels which run in the wall of the sac. After the orifice is definitely located, the intestines can be drawn through the aperture into the general abdominal cavity and the opening closed. This last step is important as recurrences have been reported which resulted from an improper primary closure. "Because of the technical difficulties produced by the distortion of the anatomy, the mortality still remains high. This can be reduced only by a more thorough grasp on the part of the operating surgeon of the anatomic anomalies at hand" (Longacre¹⁷)

SUMMARY

A case of right paraduodenal hernia is presented which, as far as could be determined, is the forty-eighth case to be reported, the twenty-ninth case to be operated upon, and the sixteenth to recover. The anatomic arrangement found was interesting not only because of the hernia present but also because of the presence of an infantile genital system, and of the position of the colon in the pelvis. The cause of the generalized adhesions in the abdomen was not determined. It is logical to believe that they were a result of an old tuberculous peritonitis as they were of the right consistency and distribution. The presence of an apical tuberculosis adds further weight to the possibility of this etiology.

We wish to express our appreciation to Dr. W. Steen, who conducted the medical management of this case and was instrumental in obtaining the patient's history.

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MANAGEMENT OF VARICOSE VEINS OF THE LOWER EXTREMITIES

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VARICOSITIES of the lower extremities are as varied in distribution and size as there are individuals presenting them. From a therapeutic standpoint, however, they can be classified simply into three comparatively distinct groups (Table I)

TABLE I
CLASSIFICATION OF VARICOSITIES OF THE LOWER EXTREMITIES

Group	Condition	
	Varicosities	Great or Small Saphenous System
I	Spider bursts, rocket bursts, telangiectatic veins	Competent
II	Mild or moderate varicosities	Competent
III	Mild moderate or marked varicosities	Incompetent

Group I—To the first group are assigned the spider bursts, rocket bursts or the telangiectatic type of veins (Fig 1). These are tiny, superficial, often interlacing vessels, complaints referable to them primarily concern their appearance. Occasionally, these vessels will rupture spontaneously. Somewhat more frequently, a sharp blow directly over the vein will produce a subcutaneous or external hemorrhage. Although not of serious import, such an accident causes considerable apprehension on the part of the patient. Elevation of the extremity affected plus external pressure over the region of hemorrhage will temporarily control the situation satisfactorily.

Group II—To the second group are assigned mild or moderate varicosities that are not associated with demonstrable incompetency of the great or small saphenous system of which the varicose veins may or may not be a part (Fig 2). If the varicosities seem to affect a portion of one or the other of the aforementioned systems, prognostication of permanent good results should be guarded, as recurrences frequently develop. This can be readily understood, for often this type of varicosity is a precursor to a general breakdown of the system involved.

Group III—The third, and most common type of varicosity, is found in approximately 50 per cent of all the patients treated for varicose veins at the Mayo Clinic. This third group is made up of those cases of incompetency of the great or small saphenous system, or both, associated with mild, moderate, or marked varicosities (Fig 3). Thus, these cases are found to be the most important, and the most exacting, with which we must deal, for it is in such

cases that we find the greatest percentage of complications of actual or potential stasis. Recurrence of varicosities due to previous inadequate obliterative therapy is also frequently noted.

General Examination Prior to Treatment—No patient should be treated for varicose veins without a complete general examination. Its importance



Fig 1

Fig 2

Fig 3

FIG 1—Diffuse spider bursts that involve primarily the lateral aspect of the lower extremity.

FIG 2—Mild and moderate varicosities on the lateral aspect of the thigh over the anterior aspect of the knee and leg; the saphenous system is not involved.

FIG 3—Incompetent saphenous system with moderate varicosities. Note circoid dilatation of the saphenous vein at the fossa ovalis.

is emphasized, further, by the fact that patients who present themselves for this kind of therapy are commonly of that age-group in which early malignant disease has its greatest incidence. When malignant lesions or other pathologic conditions are found that demand early attention, treatment for varicose veins becomes of secondary importance, and may be carried out at a subsequent date. Numerous patients may be found to have conditions of minor importance which require treatment, although elective. If the patient's condition is otherwise satisfactory, such elective therapy may be carried out in conjunction with routine obliteration of the veins.

For those individuals who are found to have pathologic lesions of the pelvis or abdomen for which treatment is not urgent, it is frequently advantageous to obliterate the varicosities first in order to lessen the possibility of postoperative superficial thrombophlebitis or other vascular accidents.

When satisfied that the patient's general condition warrants obliterative therapy, it is inexcusable not to determine the status of the deep venous circulation of the lower extremity before proceeding further. This is especially true if one can elicit a history of a previous, deep thrombophlebitis.

In our experience, very few patients have significantly incompetent communicating veins of the thigh or leg. As yet, we have not found it necessary to ligate such veins for successful obliteration of the superficial system.

Test Dose—To safely approach the obliteration of any type of varicosities, particularly those of the second and third group, a "test dose," or injection, should be given at least four hours, and preferably 24 hours, prior to therapy. We consider that 0.5 to 1 cc. of a 5 per cent solution of sodium morrhuate, or a like amount of 5 per cent solution of monoethanolamine oleate injected into a varicose vein of medium size, is the appropriate amount.

Systemic reactions seldom develop following the injection of endothelial irritants. However, if they should occur, the likelihood of minimal manifestations may be expected if small amounts are employed, as recommended for the test dose. Immediate administration of epinephrine hydrochloride has no peer in the control of these episodes. Obviously, before treatment is begun one must determine that the sclerosing solution to be employed is non-toxic to the patient.

The second important function of the test dose is to reveal information 24 hours after it is given. It is well recognized that sclerosing solutions do not react quantitatively the same among different individuals. Thus, the amount of local reaction produced at the site of injection of the test dose guides us in determining the amount of sclerosing solution to be employed at subsequent injections. This is particularly true in regard to the larger amounts used at the time of ligation and division of the incompetent vein.

Only after certain prerequisites have been fulfilled, namely, a satisfactorily general physical examination of the patient without evidence of disease of a serious nature and the selection of a nontoxic sclerosing solution, should treatment of the offending varicosities classified in Groups II and III be instituted.

Treatment—Group I—Small veins classified under Group I are obliterated primarily for cosmetic reasons. To accomplish this, infinite care must be employed to prevent further disfigurement which may easily occur if the sclerosing solution is not injected directly into the lumen of the vein. To minimize the danger of necrosis of the wall of the vein, which results in a highly pigmented scar, we use 1 to 2.5 per cent solutions of either of the previously mentioned salts of fatty acids. By vigorous shaking of the full strength solutions, surface bubbles are produced in the syringe. Injection of these bubbles may also be successfully employed to obliterate this type of varicosity (Group I).

Group II—When dealing with varicosities of mild or moderate degree without associated incompetency of the great or small saphenous system, it is rarely difficult to produce a satisfactory result. Local injections of a solution of average strength usually suffice to thrombose adequately the offending

varicosities We prefer to start at the proximal portion of the varices and proceed distally, we believe that when the proximal portion is thrombosed successfully, less solution is needed subsequently to obliterate the remaining patent portion of the vein Treatments may be carried out daily, every other day, or twice weekly at the discretion of the operator Although 2 cc of a 5 per cent sclerosing solution is approximately the average amount employed in one day, it is seldom advisable to inject this quantity at a single site unless previous experience has proved otherwise

Occasionally, it is permissible to use as much as 4 cc daily, provided that the patient's tolerance is high, or that well-scattered sites have been chosen for the injections The patient may be benefited by wearing an external support in the form of an elastic bandage during the course of injection and throughout the following few weeks The advantages of a bandage are two-fold Adequate thrombosis is facilitated, and discomfort of the patient is lessened

Group III—Obliteration of varicosities classified in Groups I and II usually offers no difficulty if the described methods are employed However, a much more extensive procedure must be instituted when the varicosities are of the type classified in Group III

We believe that ligation and division of the offending incompetent vein, and injection of a sclerosing agent into it, must be meticulously performed to obtain the greatest percentage of permanent results The advantages of such procedures are enumerated in Table II

TABLE II

ADVANTAGES OF LIGATION OF INCOMPETENT GREAT SAPHENOUS VEIN

- (1) Continuity of the vein is interrupted at its most proximal point
- (2) Possibility of canalization is reduced to a minimum
- (3) Number of local injections necessary for obliteration is decreased
- (4) Period of treatment is shortened
- (5) Adequate complete thrombosis is obtained with greater ease
- (6) Pulmonary showers are less likely to occur

It should be emphasized, at this point, that during examination, while the patient is in the standing position, not only the proper diagnosis and classification can be ascertained but, also, unusual variations and distribution of the varicosities can be noted Particularly is this true when groups of uncommon varices appear on the lateral or posterior aspects of the thighs These indicate the presence of either incompetent lateral superficial femoral veins or incompetent medial superficial femoral veins (frequently termed accessory saphenous veins) When one or the other is present, it is important to identify it at operation Treatment for such a condition is carried out simultaneously with that employed for an incompetent great saphenous vein, namely, ligation and division of the vein and the injection of a solution into its distal portion

At the examination prior to operation, it is also of value to note regions either on the thigh or legs in which great tortuosity or a localized accumulation of varicosities occurs To prevent an excessive localized reaction due to concentration of the sclerosing solution in these regions, and to procure uniform

thrombosis, binding of the thighs and the application of bandages to the legs are recommended to be used immediately following the operative procedure. The patient is advised that the binder may be removed from the thigh at any time after the lapse of a few hours. Removal of the binder may be necessary because of the considerable pain which, occasionally, may follow as the result of swelling from the underlying chemical phlebitis and periphlebitis. If there are no symptoms, the binder is allowed to remain in place until the patient is seen on the following day.

For the same reasons that a binder is applied to the thigh postoperatively, an elastic bandage is employed on the leg. The patient is instructed that the bandage may be removed whenever the extremities are elevated, that is, while in bed, the bandage should be reapplied when the patient is on his feet or in any position in which the feet are dependent. As we expect the patient to leave the hospital soon after the operative procedure is performed, it is advisable to warn him that nausea, anorexia, and a mild elevation of temperature may occur postoperatively. He is also informed that if pain, tenderness or redness occurs along the course of the treated vein, elevation of the extremity and the application of warm, moist packs will be very beneficial and will decrease his discomfort. The patient is asked to return to the clinic on the day after operation.

Technic of Division and Ligation, Technic of Injection of the Sclerosing Solution into an Incompetent Great Saphenous Vein—The site of the fossa ovalis, and, consequently, of the saphenofemoral junction, is determined after the patient is on the operating table, and draped for the operation. The point of maximal pulsation of the femoral artery at the lower border of Poupart's ligament is determined. We then measure downward, approximately one inch (2.5 cm), and then medial approximately one inch. A scratch mark is made on the skin at this site which, in the majority of instances, has proved to lie directly over the fossa ovalis. After the region has been infiltrated with a 1 per cent solution of procaine hydrochloride, an ample incision is made parallel to Poupart's ligament, the marked site of the fossa ovalis is used as the middle point of the incision. The incision is carried down to the superficial fascia and a self-retaining mastoid type of retractor is inserted.

The great saphenous vein lies beneath the superficial fascia and superficial to the fascia lata of the thigh. The superficial fascia is incised in a line parallel to that of the incision. Occasionally, blunt dissection is necessary to expose the vein when it is surrounded by excessive areolar tissue. The great saphenous vein is separated from its bed for a short distance and a curved clamp is passed beneath it.

The vein is doubly ligated with chromic catgut, and a curved forceps is placed on the vein just proximal to the ties. The vein is then divided between the ligature and the forceps, and the distal portion is allowed to retract downward.

The three uppermost tributaries of the great saphenous vein, namely, the superficial circumflex iliac, the superficial epigastric, and the external pudend-

dal veins, can be exposed by making traction on the proximal stump of the great saphenous vein and, by carefully stripping from it, with the index finger, the surrounding loose areolar tissue as far proximally as the femoral vein. These three tributaries are divided and ligated separately—this leaves the proximal stump of the great saphenous vein free of all tributaries. Two other tributaries of the great saphenous vein, the lateral and medial superficial femoral veins, are, ordinarily, not visualized in this dissection at the fossa ovalis. Occasionally, however, when one or both of these veins enter the great saphenous vein at a level higher than usual, they will be seen. When this occurs, these tributaries are treated as the aforementioned tributaries were treated and, in addition, a sclerosing solution is injected into their distal stumps. When one, or both of these tributaries are present, this essential additional procedure can be anticipated by careful preoperative examination.

By traction on the freed proximal stump of the saphenous vein with the attached forceps, the anterior surface of the femoral vein is exposed and two curved clamps are placed at the saphenofemoral junction. The great saphenous vein is doubly ligated with chromic catgut just beneath these clamps. The excess portion of the stump is excised. The ligated distal portion of the great saphenous vein is pulled upward into the wound, and the predetermined amount of sclerosing solution is injected directly into the lumen. The wound is irrigated with a saline solution and is closed with interrupted sutures.

Postoperative Care—The return of the patient to the clinic, on the day following operation, is requested, primarily, in order to assure him that he is still ambulatory. If the bandages are still on the thigh, they should be removed. If indicated, the dressings over the incision may be changed. This is occasionally necessary because of discomfort or inadequate protection. The elastic bandages on the legs are removed and are reapplied following a survey of the extent of the postoperative reaction.

The extent of the reaction is noted by inspection and gentle palpation. In most instances, the reaction extends to the level of the knee and is visible as a pink to red periphlebitis. Induration and tenderness in this region also indicate the extent of the thrombosis that has resulted. Occasionally, the reaction extends through the entire involved saphenous system, if such occurs, the necessity for subsequent injections is reduced to a minimum. In the majority of cases, however, subsequent injection of a sclerosing solution into the remaining patent varicosities must be carried out to complete the obliterative therapy. It is, usually, wise to postpone this additional treatment until the second or third postoperative day, as occasionally the maximal extent of the postoperative reaction is not obtained by the end of the first 24 hours. Should excessive periphlebitis occur during the early postoperative course, the symptoms may prevent the patient from being entirely ambulatory. When simultaneous bilateral procedures have been carried out, some increase in disability may be expected. If more than an average reaction occurs, it can be satisfactorily controlled by intermittent rest in bed, elevation of the ex-

tiemity and the application of warm, moist packs. If necessary, sedatives may be administered for a short time.

Further therapy, in the form of injecting an additional sclerosing solution, now depends entirely on the judgment of the surgeon. It is usually preferable to obliterate the remaining patent varicosities by successive, frequent injections of small amounts of the sclerosing solution, proceeding distalward.

If the cutaneous edges of the wound have been accurately approximated, the sutures are removed on the sixth postoperative day. In an occasional case, it may be wise to allow the sutures to remain in place an additional 24 to 48 hours. No wound complications have been observed following ligation of the great saphenous vein or its tributaries. We have not considered the accumulation of serum as a complication. When present, adequate drainage allows rapid subcutaneous healing of the wound.

Instructions to Patient—The patients treated for varicosities, who do not reside in the immediate vicinity of the Mayo Clinic, are usually instructed at the time of their dismissal in a special manner. A brief description of the purpose of the obliterative therapy, given to the patient at the onset of treatment, is repeated at the time of dismissal, this tends to bring about the cooperation and understanding that are necessary on the part of the patient. Soreness and tenderness of varying degrees are to be expected whenever satisfactory thrombosis has resulted in the obliterated varicosities. Usually, a period of a few days, to two or three weeks, is sufficient for most patients to accommodate themselves to these complaints. Further complaints referable to the hard, contracting, thrombosed varicosities, such as pulling, drawing or sticking sensations, stiffness, dull aches, etc., may continue for one or two months. In numerous instances, the hardness of these thrombosed veins, on palpation, continues for a year or longer, and is indicative of a satisfactory result. The patients, if forewarned, will in no way become alarmed when they first notice these hard masses. An elastic bandage, or some other suitable means of applying external support, is recommended. The length of time advised for continuing external supportive measures depends, in most instances, directly upon the extent of varicosities. The average individual will derive no benefit from such support after three or four weeks, whereas those patients who have had complications such as persistent edema of the leg, brawny induration, or ulceration may require the application of an external support for six months or a year, infrequently longer. In addition to the factor of comfort, external support is a definite aid to nature in rehabilitation of the extremity, particularly when varicosities or complications have been extensive.

The patient is further requested to return for observation, preferably six months to a year following dismissal. Frequently, at this time, a few additional varicosities or regions of recanalization may be detected. A small amount of sclerosing solution, strategically injected, will then usually permanently complete the obliterative process.

SUMMARY

From a therapeutic standpoint, varicosities of the lower extremities may be classified, simply, into three comparatively distinct groups (1) Spider bursts, rocket bursts, telangiectatic veins, (2) mild or moderate varicosities without associated demonstrable incompetency of the great or small saphenous system, and (3) mild, moderate, or marked varicosities associated with incompetency of the great or small saphenous system or with incompetency of both systems. On the basis of this classification, our method of therapy depends, and has been described. Approximately 50 per cent of patients treated have demonstrable incompetency of the great saphenous system. In such cases, the essential steps in treatment are (1) Ligation and division of the great saphenous vein at the saphenofemoral junction, (2) separate division and ligation of the tributaries of the saphenous vein, and (3) injection of a sclerosing solution into the saphenous system. Methods of preoperative and post-operative management are very important.

VISUALIZATION AND OBLITERATION OF ANGIOMATA BY RADIOPAQUE SOLUTIONS

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THE EMPLOYMENT of opaque substances to roentgenographically demonstrate hollow organs or human cavities has now become a routine procedure. While at first these media were introduced by ingestion, injection or instillation to visualize local parts, the development of nontoxic substances permitted their injection directly into the circulation in order to demonstrate remote parts. Originally, these chemicals were employed solely because of their radiopacity but as research in this field developed, newer drugs were utilized which, in addition, permitted studies of the excretory or secretory functions of the organs studied. Further investigation led to the use of substances such as thorotrast, which remain within the reticulo-endothelial system of solid organs and thus renders them opaque. Thus it is safe to say that few organs are inaccessible to roentgenographic study.

The use of opaque substances, to map vascular channels, has, hitherto, been restricted to specimens removed at autopsy, operation, or in animal experimentation. Its use *in vivo*, however, is of more recent origin and is made possible by the development of opaque substances which can be introduced into the circulation without untoward effect.

In a previous communication,¹ we demonstrated the morphologic changes which occurred in varicose veins, the character of the associated circulatory phenomena, and the existence of venous pools subjacent to varicose ulcers. A wholly fortuitous development was the sclerosing effect of the skiodan.

During the course of this investigation, we had occasion to inject several angiomata. The prompt subsidence of the tumors which followed this procedure, encouraged us to extend the study to include the plexiform and cavernous angiomata of the extremities, we refer particularly to the angiomata of muscles and not of bone, because the identification of the individual types is frequently impossible by all methods. By employing radiopaque substances such as are used in intravenous urography, we were, in effect combining several operations in one. The course and extent of the tumor could be visualized and recorded. No subsequent sclerosing media would be necessary, since vascular obliteration would frequently follow the introduction of these chemicals into the vessels. Our experience in this connection forms the basis for this communication.

Incidence—Jenkins and Delaney² studied 255 cases of muscle angiomata reported in the literature, up to 1932, and added one case of their own. It is obvious from their work as well as from our own experiences that the condition is extremely common but frequently unsuspected. Because of their

excellent review of the subject, it would be repetitious to cover the same ground here. The distribution of the cases studied by these authors is seen in Table I.

TABLE I
AGE OF PATIENT AND AGE AT ONSET OF SYMPTOMS

	Given During	Given at Onset of Symptoms and Signs
First decade	40	95
Second decade	80	67
Third decade	63	30
Fourth decade	20	7
Fifth decade	9	4
Sixth decade	2	1
Seventh decade	1	1
Eighth decade	1	1
Total	216	206

The largest individual group, therefore, occurred during the second decade. Where the age of onset of the symptoms was given however, 95 cases occurred during the first decade.

Of the 204 cases in which the sex was stated, 107 were in females. The condition occurred chiefly in the white race as only six Japanese and one Negro were included in the series. We have found that vascular diseases are uncommon in the colored people, whereas angiomas occur relatively frequently. In our group, there was a slight preponderance of the condition in the colored race. From the figures submitted by these authors, it is hard to escape the conclusion that the condition is congenital in origin, since 47 per cent occurred during the first decade in their series and in two of our cases. That trauma may be of significance is evidenced by the 17 per cent which followed injury. Four of our own cases gave a definite history of injury.

Symptoms and Physical Findings—It is difficult to diagnose this condition solely by the symptoms and physical findings. There is often a history of a slowly developing tumor, which was noted at birth or shortly thereafter. Pain is a prominent feature and is usually present but somewhat variable in character, lasting from a few minutes to a few days. Often, it may be excruciating and completely disable the patient. Pain may be present at the site of the tumor, or it may radiate down the lower extremity and resemble a sciatica. Aggravation is usually produced by walking and exercising, and relief may be obtained by any position of the extremity which tends to empty the vessels. One of our cases, however, experienced pain on standing and was relieved only by brisk walking or dancing. Trauma may cause a rupture of a vein or a localized thrombophlebitis and frequently directs the patient's attention to the tumor which has escaped his notice. The patient may develop a peculiar gait or limp due to an alteration in the length of the extremity or to direct involvement of the soft tissues. The muscles of the lower extremities are most frequently involved.

The tumor varies in size from a small nodule to an extremely large irregular mass, the size of a small orange or even larger. While its surface is usually smooth, it may at times be extremely irregular in contour or nodular. Occasionally, it is sharply defined, but more often its limits are lost in that of the neighboring muscle. The skin overlying the mass may be freely movable or attached. Port wine nevi are common and in three of our cases, dilated vessels were visible. Frequently these nevi were somewhat distant from the enlarged vascular loops. Two instances of unilateral hypertrophy of an extremity were encountered, in which vascular nevi and angiomatous dilatation of the vessels coexisted. At times, there may be an increase in the width of an extremity without any change in its length. In one of our cases, there was a slight retardation of growth of the extremity due to a mild residual poliomyelitis. In angiomata involving joint structures, there may be a marked atrophy of the contiguous soft tissues producing a fusiform swelling. Motion of a neighboring joint may be distinctly restricted or painful. In a reported case, as well as in one of our own, an anesthetic had to be administered in order to allow palpation of the tumor. In our protocols, it is described as having a spongy or rubbery consistency. Occasionally, one can feel a small nodule or an elongated area of painful induration or swelling due to a localized phlebitis which serves to direct attention to the associated angiooma. Ulceration of the skin overlying the tumor has been reported.

Diagnosis—Essentially, the roentgenographic demonstration of phleboliths in the muscles of an extremity is pathognomonic evidence of this disease, but it is important to remember that these tumors may exist without the presence of phleboliths. Occasionally, one may detect some calcification within a soft tissue tumor, or a periostitis of an adjacent bone resulting from the irritation produced by the presence of a soft tissue mass. The most accurate aid to diagnosis which we possess is the injection of a radiopaque substance in order to visualize and identify the lesion.

Technic of Administration—A preliminary roentgenogram of the part is taken in order to establish whether or not there are any phleboliths. Any syringe and needle used in the injection treatment of varicose veins may be employed and from 5 to 20 cc of a 40 per cent solution of the radiopaque chemical is sufficient for the study. The patients are prepared as for any intravenous medication. The use of the tourniquet is preferable, as some stasis of the dye in the tumor is desired. When we are assured that the needle is within the vessel, the chemical is injected slowly and without undue pressure. The limb is placed upon a cassette-changing device and toward the end of the injection, roentgenograms are taken. The needle need not be removed between exposures since it serves as a guide to the site of injection and prevents the back flow of radiopaque chemical upon the skin, where its superimposed density often masks finer vascular changes. Should it become necessary, however, to remove the needle in order to rearrange the part, a

small metallic marker may be placed as a guide at the site of injection. It is obvious that the dilution of the chemical may be very considerable in tumors of large size, and it may be necessary at times to reinject it to obtain a thorough sclerosing effect. In some tumors, however, one injection is usually adequate for visualization and therapeutic action, and in only one instance was it necessary for us to inject more than twice. In properly obliterated angiomas, it will be impossible to introduce the radiopaque chemical into the mass. Care must be exercised during the injection to assure one's self that the chemical is introduced into the angioma and not into the tissues about it, as a bad slough may develop. In none of our patients was there any untoward effect. Small angiomas in children need not be injected since they may spontaneously retrogress without treatment.

CASE REPORTS

Case 1—Hosp No 4577 L P, male, age five, was admitted, September 7, 1933, on the service of Doctor Finkelstein for a painful ulcer and swelling of the right foot. The mother stated that at the time of birth it was noted that the child had a large, soft tissue tumor involving the entire plantar surface of the foot, extending from the base of the toes to but not involving the heel, as well as a swelling below the external malleolus. At the age of eight months, the patient was taken to an hospital, where, over a period of four months, he received two roentgen ray treatments and one radium treatment. A huge blister soon developed at the site of treatment, which was incised. Excruciating pain soon developed in the extremity. He was observed monthly until the age of three, at which time further radium treatment was advised but declined. In the absence of any therapeutic response, and because of the pain which required sedation to control, amputation was advised. For the past four weeks disability has been complete and the pain agonizing.

Physical Examination—The patient was unable to walk or stand and the foot was held in the equinovarus position. There was a marked atrophy of the foot and calf. In the middle of the plantar surface of the foot, there was a large ulcerated area, measuring about one and one-quarter by one-half inches. From this area, radiating bands of scar tissue extended to the lateral borders of the foot. The ulcer was covered by an unhealthy crust which was rather firmly adherent to its somewhat edematous borders. The entire plantar surface of the foot consisted of irregular clumps of enlarged tortuous veins which extended from the base of the toes practically to the heel. The skin over these veins was extremely thin and somewhat bluish in color. On palpation the vessels were found to be of somewhat rubbery consistency and painful. The dorsum of the foot was likewise swollen (Fig 1).

The preliminary roentgenogram showed a fairly pronounced swelling of the foot. Nodular, soft tissue masses extended from the bases of the toes to the heel. On the plantar surface and somewhat centrally placed, there was a loss of soft tissue substance, representing a fairly large ulcer. Close to it and below the base of the fifth metatarsal bone, a small phlebolith was noted. On the internal surface of the fifth metatarsal bone, there was a crescentic filling defect, which extended from the base of the head of this bone, materially reducing its diameter. This was evidently due to the pressure of a soft tissue mass. On the surface of the shafts of the third and fourth metatarsal bones, a parallel periostitis was noted (Fig 2).

Because of the phlebolith, the lesion was considered an angioma, and it was decided to inject an opaque solution for diagnostic and sclerosing purposes. Under a general

anesthetic, 10 cc of skiodan was injected into the plexus of veins in the region of the base of the third metatarsal bone and roentgenograms made. These films revealed a rather bizarre picture. The opaque solution filled countless vascular loops which were present in the foot. In the main however, there were four groups of dilated vessels, two toward the lateral borders and two in the region of the heads of the metatarsal bones. The individual vessels could not be identified. At the periphery of the vascular loops, the



FIG 1—Case 1 Photograph showing the large ulcer and scar on the plantar surface of the foot. Note the distortion of the foot by irregular, nodular swellings.



FIG 2—Case 1 Preliminary roentgenogram showing the phlebolith in the region of the cuboid bone. Note the thinning of the cortex on the inner surface of the fourth metatarsal bone and of the base of the fifth metatarsal bone.

radiopaque substance produced a peculiar feathery or "hair-brush" appearance. The outlines of the bony structures were almost completely obliterated by the injected vessels (Fig 3).

The injection was followed by partial occlusion of the vessels, with reduction of the swelling of the foot. In view of the favorable result, the procedure was repeated three weeks later, using 2 cc of a 5 per cent sodium morrhuate solution but selecting on this occasion the plexus beneath the external malleolus for injection. Three subsequent injections of sodium morrhuate were employed to occlude isolated groups of veins. Following the use of the sclerosing medium, there was a temporary copperish discoloration of the skin which quickly subsided. Within ten days, the pain had disappeared. In six weeks, the ulcer had healed and the patient was able to walk about and soon engaged in the usual normal activities of a boy of his age. Subsequent attempts to reinject the larger vessels were unsuccessful because they had been completely occluded. Figure 4 is a photograph of the foot taken three years after treatment. This patient was seen about six months ago, at which time a few small, patent vessels were still present between the first and fifth metatarsal bones but these were symptomless and too small to require further treatment.

Case 2—Hosp No J-8127 T G, male, age three, was seen July 21, 1937. The

mother stated that the child has had "red spots" and irregular painful swellings in the right forearm and hand since birth

Physical Examination—Flat, fluctuating masses were felt on the dorsal surface of the right forearm at the junction of its middle and distal one-third. These masses measured about one and three-quarter inches in diameter, were somewhat sensitive and apparently not attached to the bones. Many dilated veins were noted on the palmar surface of the hand. The skin was somewhat bluish in color and redundant as though frequently stretched. There were no evidences of acute inflammation. The Kahn and tuberculin tests were negative.



FIG 3—Case 1. Roentgenogram after injection of skiodin showing all the bony landmarks obscured by the radiopaque solution in the vascular loops. Feathery "hair brush" appearance of vessels.



FIG 4—Case 1. Photograph three years after injection showing the scar replacement of the original ulcer and the restoration of the contours of the foot.

Preliminary roentgenologic examination showed the right ulna slightly increased in width. The medullary canal was ill-defined and in the middle one-third of the shaft was obliterated, whereas in the proximal one-third it appeared to be slightly expanded. The cortex was thinned out, somewhat irregular in contour, and, in scattered areas, split longitudinally. The periosteum was irregularly thickened. In the soft tissues of the forearm at about the level of the junction of its middle and distal one-third and somewhat posteriorly placed, there was a fusiform soft tissue swelling within which a phlebolith was visualized. The shafts of the third, fourth, and fifth metacarpal bones as well as the proximal phalanx of the fourth finger showed changes identical with those in the ulna. Numerous other bones of the skeleton were examined and found to be negative.

On November 7, 1935, large veins on the volar aspect of the forearm were distended by means of a tourniquet and 6 cc of diodrast injected. Roentgenograms, taken immediately, showed numerous, fairly large clumps of vessels in the soft tissues of the forearm from its middle one-third to the elbow joint posteriorly. Identification of the individual loops was impossible. Several scattered phleboliths were noted (Fig 5).

Examination of the forearm, one week later, showed the masses to be definitely harder and the veins less prominent. There were still, however, several dilated veins in the lower end of the forearm and these were injected with 2 cc of sodium morrhuate.

Shortly thereafter 6 cc of diodrast were again injected in order to map out the tumor. The roentgenogram revealed a somewhat elliptical group of vessels on the inner and posterior surfaces of the forearm extending from the level of the styloid process to the middle of the ulna. Some of the collateral vessels were outlined but the main stream of the dye detoured around, but did not fill, the preexisting tumor. It was apparent, therefore, that it had been completely sclerosed (Fig 6).

Examination of the patient, three weeks later, showed that the tumor of the forearm had been completely obliterated, pain had disappeared, and the nevus was lighter in shade.

Case 3—Hosp No 66079 A B, colored, female, age three, was admitted August 14, 1937. The mother stated that since birth she had noted a smooth tumor of the left lower extremity which grew slightly as the child developed. Although there was no pain while at rest, the child complained at times after walking short distances. The mother stated that she herself has had a positive Wassermann for the past two years. Blood

and spinal Wassermann examinations on the child done elsewhere, however, were reported negative.

Physical Examination—The lower extremities were of equal length but the circumference of the left leg measured eight inches, whereas that of the right leg measured seven and one-half inches. On the anterior surface of the left leg, there was a hard, irregular swelling which seemed to be adherent to the skin. There was, likewise, a swelling on the internal and dorsal aspects of the foot but this swelling was softer than the mass in the leg and definitely movable. Lymph nodes could be palpated in the cervical, inguinal, axillary, and epitrochlear regions.

Roentgenologic examination disclosed an irregular soft tissue mass at the level of the middle one-third of the left leg anteriorly, which appeared to extend backward into the muscles of the calf. There was, likewise, a soft tissue swelling on the dorsum of the foot, which extended to its lateral borders. There was no disease in any of the bones of the left leg or foot.

Because the condition had existed since birth, the presence of the adenopathy, and since the mother was a known luetic, it was considered syphilitic in origin. Accordingly, 0.12 Gm of neosalvarsan was administered in-

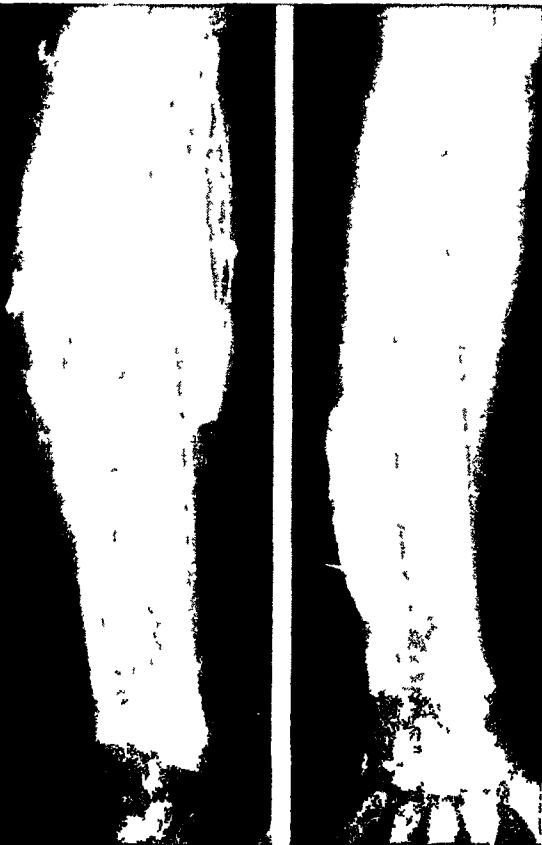


FIG 5—Case 2. Roentgenogram after injection of diodrast showing innumerable dilated vascular loops. Note the soft tissue swelling in this area.

FIG 6—Case 2. Roentgenogram after injection of lower group of dilated vessels. Note that the original tumor has been obliterated, and the main stream of the dye detours around the preexisting tumor.

travenously and shortly thereafter, 0.5 cc of bismuth subsalicylate was given twice weekly for several weeks. The Wassermann and Kahn tests, twice repeated, were pronounced negative, but despite this fact the antiluetic therapy was continued. About this time, the results of a previous biopsy of the mass, performed at another hospital, were communicated to us. The interpretation of that section was "chronic granulomatous tissue." The patient was discharged October 6, 1937.

On October 15, 1937, the child was readmitted. At this time, there was a fairly pronounced limp, and edema of the left lower extremity. The circumference of the left leg at this time was eight and one-half inches and of the right leg, seven inches. Antiluetic therapy was again instituted. Roentgenologic examination, at this time, disclosed a pyriform, circumscribed soft tissue mass on the posterior and internal aspect of the calf. There was no involvement of the underlying tibial shaft. Because of our previous experience, the suggestion was made that we might be dealing with a muscle angioma. After a period at the hospital, during which antiluetic treatment was continued, the patient was discharged unimproved.

On February 7, 1938, the patient was admitted for the third time. The mother stated that for a time since the previous discharge the child had felt quite well. The swelling of the left leg had practically disappeared and the child had been able to carry on the usual activities of a youngster of this age. About two weeks ago, however, the left leg and foot became swollen overnight. Although there was no definite discomfort at first, the pain during the last few days, however, had returned and become increasingly severe.

Physical Examination, at that time, revealed a generalized swelling of the left lower extremity from just above the knee joint to the toes. There was, in addition, local swelling behind and below the malleoli. There was a scar over the middle of the tibia on its anterior aspect. At the upper portion of the scar, there was a little thickening, and about two inches below the spine of the tibia, overlying the crest, there was a small hard mass measuring about one-half by three-eighths of an inch, attached to the skin and freely movable on the underlying tissues. There was a generalized swelling of the leg. Two discrete, slightly tender masses were noted behind the external malleolus. In both groins, there were rather discrete, shotty, lymphadenopathies. No epitrochlear nodes were felt but there was a slight axillary adenopathy. Again, antiluetic therapy was advised. In the absence of all therapeutic response, a biopsy was performed February 9, 1938. The surgical pathology showed "Underlying the skin, was found a firm mass which was completely encapsulated and which could be bluntly dissected from the surrounding tissues. At the upper pole of the mass, a nerve was seen running into it. This mass was split and the nerve followed through its entire course into, through, and out of it. It was possible with extreme care to free the nerve completely from the mass. Within the tumor, were areas of old hemorrhage and cysts containing clear straw-colored fluid. Bleeding was easily controlled."

The report of the section removed at operation (Path No B-18593) was "diffuse angiomatosis of the leg." About a fortnight later 20 cc of hippuran was injected into the mass of veins on the dorsum of the leg. The roentgenogram revealed a generalized, diffuse dilatation of the vessels of the calf as well as in the popliteal area. Small, circular densities suggested the presence of phleboliths (Fig 7).

The patient was seen in October, 1938. There was an excellent result from the injection, most of the dilated veins had been obliterated but there was still present a few radicles in the foot which were to be further treated but the patient disappeared from observation.

Case 4—Hosp No F-07085. H. B., male, age 17, was seen May 28, 1934. The patient stated that he had been struck on the inner and posterior surfaces of the left elbow joint, 14 years previously, and that four months later, he developed a soft tissue swelling in this area which had progressively enlarged.

Physical Examination revealed a lobulated, semielastic mass on the ulnar surface of the elbow joint and extending as far forward as the interosseous ridge of the humerus. This mass appeared to contain fluid and seemed to communicate with the elbow joint. Supination and pronation were slightly, if at all, limited. The ulnar nerve could be felt running through the tumor and it appeared to be displaced from its normal bed. Pressure

over the swelling caused a typical ulnar nerve response but there was no evidence of ulnar nerve paralysis. The Wassermann and Kahn tests, performed immediately after admission, were negative.

Roentgenologic examination revealed a fusiform, soft tissue mass on the ulnar surface of the forearm extending from the internal condyle of the humerus to the distal one-third of the ulna. Within this tumor, several phleboliths were demonstrated. There was some irregularity in the cortex of the ulna adjacent to the mass.

On July 9, 1934, the patient was operated upon and "a huge mass containing bloody fluid was encountered. As soon as dissection was started, a great deal of bleeding resulted. As the muscles were divided, a large cavity was found extending from the epicondyle down to the lower one-third of the forearm on its medial aspect. There were no veins or any other abnormal tissues in the cavity except two rounded masses, one having the color of a rice body and as large as a pea and, the second, black in color and about the size of a lentil."

Pathologic Examination—Section showed numerous bits of muscle and collagenous tissue. The larger lobulated body was a thrombus. Numerous thicker- and thin-walled blood vessels were seen.

Pathologic Diagnosis "Intramuscular hemangioma."

Accordingly, shortly thereafter, 10 cc of skiodan was injected into a prominent vein in the upper one-third of the forearm and roentgenograms made, which showed large clumps of dilated vascular loops on the inner aspect of the forearm in its proximal third. The upper limits of the mass reached the external condyle of the humerus and its outer edge was in intimate contact with the shaft of the ulna. Within the tumor, were numerous phleboliths which had been visualized previously (Fig 8).

The patient was examined about one week later, and the tumor was found to be definitely smaller, and an additional 10 cc of skiodan was injected. A subsequent attempt to reinject the vessels was only partially successful, as they were practically completely obliterated (Fig 9). The patient was last seen about one year later and, at that time, the mass was considerably reduced in size, the vessels completely obliterated, and pain had completely disappeared.

CONCLUSIONS

By injections of radiopaque solutions, such as are commonly employed in intravenous urography, angiomas may be visualized and roentgenographically re-

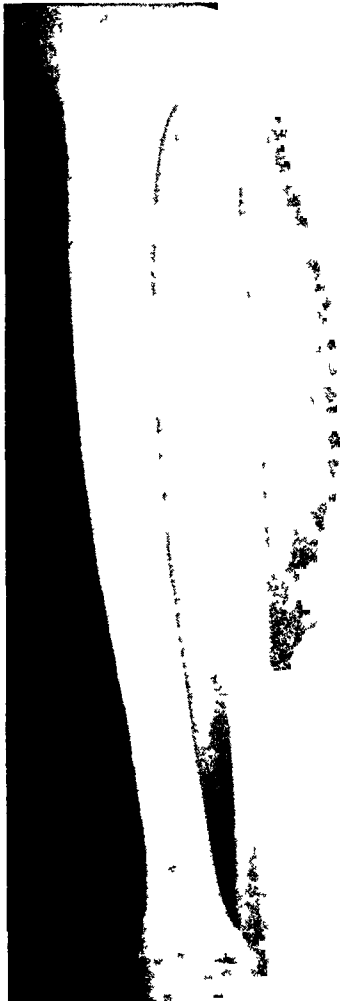


FIG 7—Case 3. Roentgenogram after injection of hippuran showing diffuse dilatation of the vessels of the leg. Note the numerous phleboliths.

recorded. Although these chemicals possess sclerosing properties, they are best utilized for diagnostic purposes, and to determine the extent of

sclerosis following the injection of obliterating media. By the use of these chemicals, open operation may be avoided and satisfactory relief obtained.



FIG 8—Case 4. Roentgenogram after injection of skiodan illustrating localized dilatation of vessels. Radiopaque substance obscures the phleboliths.



FIG 9—Case 4. Roentgenogram one week after Figure 8. Second injection of skiodan fills only the superficial vessels. The large tumor is obliterated. Note the phleboliths.

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ACTIVE IMMUNIZATION AGAINST TETANUS

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CHESTER, PA

RAMON and others²⁻²³ have proposed that vaccination with tetanus toxoid be employed as a routine public health measure in order to overcome the well known limitations of passive immunization and to provide a permanent immunity against tetanus

Naturally, the first question that arises is how much antitoxin must be present in the blood to insure against the development of tetanus in the presence of a wound infected with *Cl tetani*? No one knows. Animal experiments are inconclusive. Sneath, Kerslake, and Scruby¹ injected a lethal spore dose into a group of 55 guinea-pigs actively immunized by means of tetanus toxoid and found that 80 per cent of the animals were completely protected, 11 per cent were partially protected, and 9 per cent died of tetanus. From their studies it would appear that in the guinea-pig, the level of 0.01 unit of tetanus antitoxin per cc of serum is a critical level in active immunization. Above that level, in 45 animals 13 per cent showed signs of tetanus, from which they recovered, while the remaining 87 per cent were completely protected.

The incidence of localized tetanus in 13 per cent of the immunized animals is, however, worthy of emphasis since in the human being, one must strive for complete protection in all cases.

In a similar type of experiment Cowles² encountered the same inconsistency in the antitoxin level required for protection as noted by Sneath and concluded that although it is probably impractical to define the minimum titer which will assuredly protect against tetanus, antitoxin values of 0.10 or 0.20 unit per cc of serum can give a fairly certain protection in immunized guinea-pigs and mice at the time of infection. This author felt that though 0.10 unit is not sufficiently great to protect all animals against a maximum infection, it is probably much larger than is necessary to care for many infections resulting from wounds judged to be too slight for surgical attention, and probably large enough to care for the majority of injuries that receive surgical treatment.

Bergey and Etris^{3, 4} have suggested that 0.01 unit may be satisfactory for protection. In a later publication⁵ these workers maintain that 0.01 unit is "the least amount of antitoxin necessary for protection and is based on the finding in the serum of the person who showed least response to the antigenic effect of the toxoid one year after the second dose. This individual had 0.01 of a unit of tetanus antitoxin." This finding cannot, however, be accepted as indicating the protection level against infection.

We believe that, in the present state of our knowledge, active immunization must, to be of value, engender at least a titer equivalent to that produced

by the subcutaneous injection of 1,500 units of tetanus antitoxin. Serial titrations done by us⁶ after such a prophylactic injection revealed the presence of 0.10 to 0.25 unit of antitoxin per cc of blood serum (Chart 1). Hence we consider 0.10 unit as the minimum required for protection. It may be argued that this level is too high since less than 1,500 units may suffice for

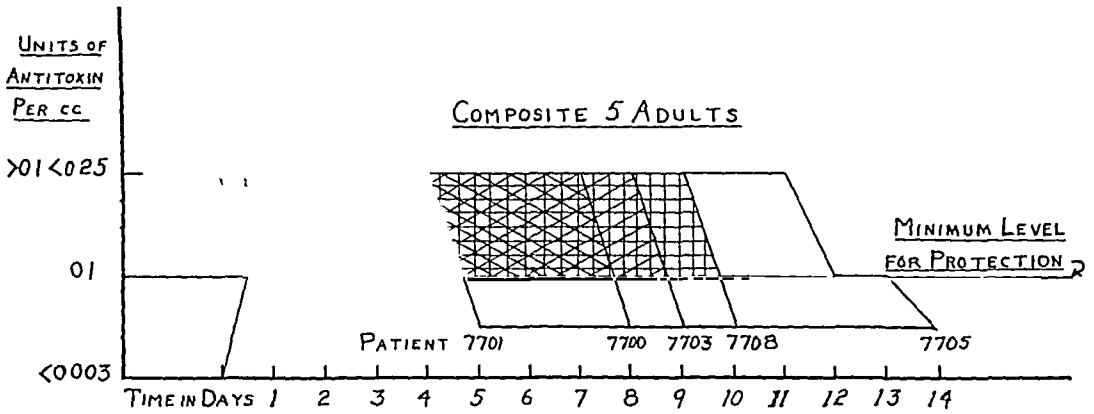


CHART 1—Showing duration and extent of passive immunization following administration of 1,500 units of tetanus antitoxin

passive immunization. Yet we feel that until direct and conclusive evidence exists on this point it is safer to err on the side of conservatism, and propose that no subject be considered immune unless he has at least 0.10 unit of antitoxin per cc of serum following the injection of a primary course or "repeat" dose of tetanus toxoid.

Method of Immunization—Two types of antigen are now in use. In France and Canada the plain tetanus toxoid is employed. The entire French Army as well as many thousands of civilians have been immunized with three doses of 1.0, 1.5 and 1.5 cc of the plain toxoid given at intervals of three weeks. This schedule produces, according to Ramon, a high-grade immunity which lasts several years^{7, 8, 9}.

In England, the Royal Air Force has been immunized with two 1.0 cc doses of plain toxoid given about six weeks apart¹⁰. This schedule is based upon Boyd's¹¹ observations that two doses of plain toxoid given six weeks apart are as effective as three doses given at close intervals. In the United States, tetanus toxoid, alum-precipitated, has been used almost exclusively. Jones and Moss¹² working with both plain and alum-precipitated toxoids found that two injections of the alum preparation produced a greater and quicker immunity than three injections of the plain toxoid. Similar results were obtained by us¹³. We also found that the dose, the potency of the alum toxoid, and the interval between injections were important factors in determining the height and duration of the titer produced. Thus, when we¹⁴ compared two series of patients that received different doses of the same lot of alum toxoid we found that at the end of 91 days after the second dose only 11.7 per cent of the group that received two 1.0 cc doses dropped below 0.1 unit while in the 0.5 cc group 42.8 per cent of the subjects showed less than 0.1 unit. At the end of 181 days 53.3 per cent of the 1.0 cc group had less

than 0.1 unit while 75 per cent of the 0.5 cc group dropped below this value. It is obviously not a question of volume alone but also of the antigenic potency of the volume injected. Thus 0.5 cc of one lot of toxoid may be equivalent in potency to 1.0 cc of another lot. The official standard for tetanus toxoid* is a minimum standard, and commercial preparations available on the market vary considerably in their potency.¹⁵

The length of time allowed to elapse between the two injections of alum toxoid is of definite importance. When the second injection of 1.0 cc of alum toxoid was given by us one to four weeks after the first dose,⁶ we failed to note any appreciable increase in titer. If given beyond this period a prompt and decided rise in titer occurred. McBryde,¹⁶ Hall,¹⁷ and Cowles² gave the two injections at intervals of 73 days, six weeks and 11 weeks, respectively. We prefer to inject them about three months apart because we feel that the longer interval favors the development of a higher antitoxic titer. Jones and Moss²³ have recently expressed a similar belief, although they had allowed a one month interval between the two injections.

Antitoxic Immunity—The first injection of 1.0 cc of alum toxoid does not result in any appreciable increase in the titer of most subjects. Only an occasional patient shows a rise to 0.1 unit. Apparently the first dose of toxoid prepares the antitoxin-producing cells in such a way that following injection of the second or subsequent doses there occurs a rather prompt release of antitoxin. This takes place even after five years have elapsed between the two injections. Age, sex, and color do not affect this mechanism. We have found that an acute infectious process such as lobar pneumonia interferes with the development of antitoxin while syphilis (latent) and active allergic states such as hay fever and bronchial asthma do not.

After the second injection, values of 0.10 to ten units per cc of blood serum have been reported by us, and others^{2 to 6 and 12 to 23}. To obtain equivalent titers would require the injection under the skin of many thousands of units of antitetanic serum (Table I). Naturally the rate of development of this protective titer is of utmost importance. After the second injection, five to 14 days may elapse before 0.1 unit of antitoxin appears in the blood. The maximum values are obtained at the end of one month. Thereafter, a loss in titer occurs which is most marked during the first three to six months. Some subjects show less than 0.10 unit at the end of three months but the great majority do not drop below this level until after six months. A few retain a good protective titer for more than two years. In the last seven years we have encountered only one refractory subject but he responded well to a third injection. Individual variations in antitoxin response are very prominent. Because of this and the absence of a simple test to determine the state of antitoxic immunity, it is necessary to raise the antitoxin titer of the blood to a protective level at the time of injury.

* A human dose (0.5 or 1.0 cc) injected subcutaneously into guinea-pigs of 500 Gm weight, shall, in a period of four to six weeks, engender at least two units of antitoxin per cc of serum.

TETANUS IMMUNIZATION

TABLE I

TETANUS TOXOID, ALUM-PRECIPITATED

Basic (Primary) Course Two 10 Cc Doses given 90 Days Apart

Number of Subjects Tested	Time After Second Dose	Titers in Units of Antitoxin Per Cc of Blood Serum Number of Subjects							Percentage of Subjects with 0.10 Unit or More
		-0.10	0.10	+0.10 -0.25	0.25 to 0.50	0.50 to 1.0	1.0 to 3.0	3.0 to 10.0	
14	1 wk	4	1	1	8*	—	—	—	71.4%
16	2 wks	—	—	—	13†	—	2	1	100%
153	1 mo	—	3	19	14	29	71	17	100%
60	3 mos	5	6	—	24	18	6	1	91.6%
59	6 mos	17	11	13	13	4	1	—	71.1%
50	9 mos	21	18	4	4	2	1	—	58.0%
39	12 mos	17	15	3	3	1	—	—	56.4%
30	20-22 mos	21	3	2	3	1	—	—	30.0%

* Six subjects had +0.25 unit

† Eleven subjects had +0.25 unit

+ More than

— Less than

Secondary Stimulation—"Repeat" Dose—In 1927, Ramon called attention to the value of the injection "*de rappel*" Since then it has been definitely established that the injection of a third "repeat" dose of alum toxoid (secondary stimulus) will effectively raise the titer above the level of protection. Titers of 0.25 to more than ten units have been reported after such a "stimulating" dose.^{2, 13, 18, 21, 23} Again, the rate of increase of the titer is of the utmost importance. To be effective the increase must be rapid, before the incubation period of tetanus expires. The latter is usually given as from six to 14 days and is directly proportional to the amount of toxin and the severity of the disease. We²¹ have found that five to seven days elapse after the "repeat" injection before a titer of at least 0.1 unit appears in the blood (Table II). This should prove satisfactory since we are dealing here with an

TABLE II

TETANUS TOXOID, ALUM-PRECIPITATED

Antitoxin Response to a "Repeat" Third Dose (10 Cc) given Nine to Twelve Months After Completion of Basic Course of Immunization

Number of Subjects Tested	Time After Third Dose	Titers in Units of Antitoxin Per Cc of Blood Serum Number of Subjects							Percentage of Subjects with 0.1 Unit or More
		-0.10	0.10	+0.10 -0.25	0.25 to 0.50	0.50 to 1.0	1.0 to 3.0	3.0 to 15.0	
1	2 days	1	—	—	—	—	—	—	0%
5	3 days	4	1	—	—	—	—	—	20%*
14	4 days	12	—	1	1	—	—	—	14.2%
16	5 days	1	2	2	5	1	5	—	93.7%
7	6 days	1	—	1	2	—	3	—	85.7%*
24	7 days	—	—	—	2	2	11	9	100%
31	1 mo	—	—	1	2	3	13	12	100%
27	3 mos	—	—	1	6	6	12	2	100%
28	6 mos	3	2	3	7	8	5	—	89.2%
21	9 mos	3	3	3	4	5	3	—	85.7%
19	12 mos	3	2	3	7	4	—	—	84.2%
15	15-19 mos	5	—	4	5	1	—	—	66.6%

* Percentage irregularity accounted for by small number of subjects tested

+ More than

— Less than

active immunity that is actually on the increase. It has also been reported by Jones and Moss,²³ and by us,²¹ that after injection of the "repeat" dose there is a tendency for the titer to be retained over a longer period of time than after the basic course of immunization. This is well illustrated by a comparison of the titers in Tables I and II.

McBryde¹⁶ and others^{11, 41, 42, 43} have suggested that if the wound of an immunized subject became infected with tetanus spores, protection would be maintained by an outpouring of antitoxin in response to the first threat of invasion by toxin. If true, this would be of tremendous value because it would make any further "repeat" injections of toxoid unnecessary. No human observations exist on this point. Jones and Jamieson²⁴ found that a massive dose of tetanus spores did not markedly accelerate the production of antitoxin in guinea-pigs that had been previously immunized with alum toxoid. Some of the animals had as high as four units and yet they developed localized tetanus from which, however, they recovered. Boyd¹¹ interprets Jones's results differently. He argues that the titer in the test animals was so high that it is probable that the toxin produced by the germinated spores was immediately neutralized and failed to reach the reacting mechanism in a form capable of provoking antitoxin production. Wolters and Dehmel²⁵ have presented experimental evidence that actively immunized animals may survive spore infections with production of increased titers. In a very interesting study, Zuger, Greenwald, and Gerber²⁶ found that guinea-pigs immunized with a single injection of 1 MI of tetanus toxoid will react subsequently with an increased antitoxin titer when infected with a lethal dose of spores. The rise in titer will first be evident on the seventh day after infection in some of the guinea-pigs, especially in those that are without symptoms or if with symptoms, in those that will recover. This rise is small, a significant one not taking place until the eighth to tenth day, in contrast to the significant rise in titer that takes place on the fourth to fifth day when similarly prepared animals are given toxin instead of spores. They also found that when an additional dose of toxoid is injected simultaneously with the spores, a significant rise in titer is evident on the fifth day. The authors concluded that there is no evidence that the increase in titer induced by infection with spores can have sufficient protective effect, as hoped by some.^{16, 42, 43}

From these studies it is clear that a "repeat" injection of toxoid should be given whenever an injury occurs.

Associated and Combined Immunization—The French were the first to call attention to the possibility of simultaneous immunization against several diseases by the injection of mixed antigens. Ramon and Zoeller,^{7, 27} and Sacquepee, Pilod, and Jude^{28, 29} have reported on the use of an "associated" triple vaccine against typhoparatyphoid fever, diphtheria and tetanus. Immunization was accomplished by the injection of three doses of this triple vaccine followed by an injection "*de rappel*" for the purpose of reenforcing the diphtheria and tetanus antitoxin titers. In this country Jones and Moss^{22, 23} have reported on the use of a combined diphtheria and tetanus toxoid, alum-

precipitated They found that a good basic immunity was established by this mixed antigen and that its injection as a stimulating dose produced not only an immunity that was much greater than that obtained with the two primary injections but one that was prolonged over a much greater interval They also found that the combined toxoid did not interfere with the specific immunity response to each disease

In addition to this "associated" immunization against several distinct diseases, Ramon³⁰ has also proposed the use of the combined active and passive method of immunization for the prophylaxis and treatment of tetanus He found that active antitetanic immunization could be realized by the simultaneous injection at the time of injury of both antitetanic serum and toxoid, followed by two doses of toxoid alone, at intervals of two or three weeks Patients treated by serovaccination have the same antitoxic response to a subsequent "reenforcing" dose of toxoid injected several months or a year later, or later still, as patients who had been vaccinated with toxoid alone These findings have been confirmed by Sacquepee and Jude^{31, 32, 33}

In the presence of tetanus, Ramon, *et al*,³⁴ advise the administration of "150,000 I U of antitetanus serum and 2 cc of tetanus toxoid given in different sites Gradually progressive doses are then repeated at intervals of five or six days—2, 4 or 6 cc of toxoid for instance Later, 'reenforcing' doses of toxoid may be given, they are harmless and of real benefit Ramon stated that experimental investigations and clinical tests made upon patients brought evidence that active immunization due to injections of toxoid follows without interruption of the passive immunization due to serotherapy" This observation is of crucial importance because of the possibility that the injected antitoxin serum (passive immunity) would neutralize the toxoid *in vivo* and thus interfere with the development of an active immunity Complete agreement on this question does not exist as yet Thus, Otten and Hennemann³⁵ have recently reported that active immunity induced in the guinea-pig by formol toxoid appears to be inhibited by the presence of passive immunity They found that the third to sixth week constitutes the critical period because at this time passive immunity becomes exhausted while active immunity has not reached the required level We are now investigating this problem

Secondary Stimulation by the Intranasal Route—Because tetanus toxoid must be injected repeatedly for stimulating purposes, we have investigated the possible use of other routes for the administration of the antigen We^{15, 36} have found that after a basic (primary) immunity has been established by the injection of two doses of alum toxoid given three months apart, we are able to raise the antitoxin level of the blood by the instillation in the nose of a specially prepared tetanus toxoid (Topagen*) The administration of two to three drops (about 0.1 cc) of tetanus toxoid Topagen in each nostril on three successive days will raise the antitoxin titer to a protective level (0.1 unit or more) in seven to 14 days (Table III)

* Manufactured by the Mulford Biological Laboratories, Sharp & Dohme

TABLE III

INTRANASAL STIMULATION WITH TETANUS TOXOID TOPAGEN

Three Daily Intranasal Instillations Given in Lieu of a Third "Repeat" Injection Seven Months After Completion of the Basic Course of Immunization

Antitoxin Response 14 Days After the First Instillation

Number of Subjects Tested	Control* Titer	Titer in Units of Antitoxin Per Cc. of Blood Serum After Intranasal Stimulation Number of Subjects							
		0 10	+0 10 -0 25	+0 25 -0 50	+0 50 -1 0	+1 0 -3 0	+3 0 -5 0	+5 0 -10 0	+10 0 -15 0
90	-0 10	1	9	17	20	27	12	4	—
5	0 10	—	—	2	—	3	—	—	—
26	+0 10	—	—	4	7	7	5	2	1
	-0 25								
9	+0 25	—	—	—	—	4	3	2	—
	-0 50								

* Control bleeding obtained just before first instillation

+ More than

— Less than

The nasal treatments should be repeated every six to 12 months in advance of an injury. Experience to date, covering a large series of subjects that have been followed-up for more than a year, suggests that this combined method of active immunization by the subcutaneous and intranasal routes is a safe, simple, and effective means of producing and maintaining a solid immunity against tetanus. Its advantages are obvious.

Reactions—The injections of tetanus toxoid, alum-precipitated, produce in many subjects a local reaction that varies in intensity. This local inflammatory response is more prone to occur if the toxoid is injected superficially under the skin, and is apt to be more intense after repeated injections of toxoid. It usually subsides in 24 hours. Occasionally, there is an associated aching and malaise. The most important reaction encountered is that due to sensitization. This may assume the form of anaphylactic shock, urticaria, or bronchial asthma. The French,^{7 8 9} whose experience covers many hundreds of thousands of injections, have failed to report any untoward reaction. The British^{10 37} have encountered two cases of nonfatal anaphylactic shock following the second injection of plain tetanus toxoid. Both patients gave positive skin tests to Witte peptone which was present in the injected toxoid. In this country, Cooke³⁸ has called attention to the sensitizing properties of alum toxoid due to the presence of peptones and has reported several instances of allergic reactions such as asthma and hives following the second injection of alum toxoid. He recommended the use of a synthetic medium for the growth of *Cl. tetani* and the routine performance of skin tests prior to the toxoid injection. We³⁹ have reviewed the collective experience of several workers in this field and found only two cases of urticaria in over 1,700 immunizations with two or more doses of alum toxoid. Similarly, Hall,⁴¹ in a review of his large experience at the U. S. Naval Academy, encountered four instances of urticaria and one of frank anaphylactic shock among 1,800 subjects that had received a second dose of "inadequately washed," alum-precipitated, tetanus toxoid. No reaction occurred following the injection of a

second dose of a well prepared toxoid in 1,293 additional subjects. Hall concluded that an alum-precipitated toxoid, thoroughly washed, is a safe immunizing agent and should not produce reactions of sensitization. The paucity of reports of clinical sensitization is in marked contrast to the high frequency of positive skin tests to the various components of the toxoid (especially to the peptone) obtained by us³⁹. Moreover this lack of correlation between the skin and the clinical evidences of sensitization is further illustrated by our ability to administer to four patients a full dose of tetanus toxoid, alum-precipitated, in the presence of marked positive skin tests without any untoward reaction. Actually, two of the subjects were asthmatic children. Hence, we feel that skin tests with tetanus toxoid are not a reliable guide for the detection of clinical sensitivity which may occasionally develop following injection of the toxoid. As in any other immunizing procedure epinephrine HCl should be kept on hand for the control of any reaction. In this respect, it is perhaps worth while to recall the fact that in 1927 Ramon and Zoeller⁴⁰ reported on the successful use of the intranasal route for immunization against diphtheria in subjects that were extremely sensitive to diphtheria toxoid and could not tolerate its injection.

CONCLUSIONS

Active immunization against tetanus is both practical and safe. A basic (primary) immunity can be established by the injection of two doses (0.5-1.0 cc) of alum-precipitated or plain toxoid given about three months apart. Thereafter, a "repeat" injection of toxoid (1.0 cc) should be given whenever an injury occurs. This will serve to raise the antitoxin level of the blood of the immunized subject to a protective level. In lieu of these "repeat" injections, intranasal instillations of tetanus toxoid Topagen (0.1 cc in each nostril, on three successive days) can be given with advantage. These instillations should be repeated periodically every six to 12 months. They will then produce a solid immunity against tetanus, in advance of an injury. It also appears that immunization against tetanus, diphtheria, and typhoid fever can be accomplished simultaneously by the injection of a mixed antigen.

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THE INFLUENCE OF TEMPERATURE ON WOUNDS

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THE USE of local applications of heat or cold for the treatment of disease is as old as recorded medicine. Hippocrates recommends the application of heat by fomentation for the relief of pain in "acute disease" but warns that if the pain is not relieved, one ought not to foment for a length of time because this dries the lungs and promotes suppuration. Within comparatively recent times, hot poultices of a great variety of composition constituted a very large part of the therapeutic methods employed, but the faith in the efficacy of the substance or drug composing the poultice largely gave way to the opinion that any beneficial effect of the poultice was solely due to the fact that it was a means of local application of heat.

Although some practitioners of medicine still believe that hot and cold applications each have their peculiar indications, most physicians probably agree with John Hunter that neither hot nor cold applications have any considerable influence on the development of any pathologic process. There is ample evidence for the truth of this statement in the frequency with which practitioners of medicine state that the choice of hot or cold applications, as well as the method employed, is dependent solely on the comfort derived by the patient.

In a previous publication¹ the authors have reported an experimental study in which it was shown that temperature was an important factor in determining the length of survival of living tissues completely deprived of circulation. The purpose of this paper is to report the results of an experimental study of the influence of temperature on the reaction of living tissues to injury.

The first experiments consisted in performing, with careful aseptic precautions, abdominal incisions in dogs, in some of which the wound was contaminated by a standard dose of a broth culture of *Staphylococcus aureus*. Contaminated wounds and presumably uncontaminated wounds were permitted to heal at body temperature, and a number of both types of wounds were subjected to both hot and cold applications during the period of healing. These experiments showed a very marked influence of temperature on both the gross and microscopic characteristics of the healing wounds. All of these experiments, however, were discarded because of the lack of complete control over such factors as unknown bacterial contamination, differences in degree of hemostasis, differences in interference with blood supply to tissues, and differences in amount of trauma inflicted, which would not only vary in different wounds but in the different parts of the same wound. The experimental method employed in the experiments forming the basis of this paper not only excluded the uncontrollable factors necessarily associated with an

abdominal incision, but produced a wound sufficiently small for the entire diameter of the wound to be included in a single microscopic section

Dogs were used as the experimental animal. Since it was necessary to restrain the animal throughout the entire course of the experiment, anesthesia was constantly maintained by repeated subcutaneous injections of morphine sulphate. After the removal of the hair from the entire back, the skin was cleaned with green soap, iodine and alcohol. Three pairs of symmetrical points were chosen so that two of these points could be subjected to the application of heat and two to the application of cold, while the third pair was not influenced by either hot or cold applications. At three of the points chosen, 0.1 cc of oil of turpentine was injected intracutaneously with a No. 27-gauge hypodermic needle. At the other three sites chosen, 0.1 cc of a 24-hour broth culture of *Staphylococcus aureus* was similarly injected. The *Staphylococcus aureus* used was obtained from a culture which had been propagated in the laboratory for a period of years, during which time it had maintained a constant virulence.

To each side of the animal's back was fitted a thin rubber bag which covered two areas of injection—one of turpentine and one of *Staphylococcus aureus*. The remaining two sites of injection, one of turpentine and one of *Staphylococcus aureus*, were placed sufficiently far away so as not to be influenced by any alterations in temperature from the rubber bags. An appropriate system of tubes and electric pumps maintained a constant circulation of cold water through one bag and hot water through the other. Frequent measurements of the temperature at the point of contact between the rubber bag and the skin showed that on one side the temperature remained at approximately 10° C, while on the opposite side the temperature remained at 40° C. All of these experimental lesions were as superficial as it seemed possible to produce a lesion appropriate for this study. Since all of the tissues studied

EXPLANATION OF PLATES

PLATE I, FIG. 1—Actual size color photograph of a lesion 48 hours after the intradermal injection of 0.1 cc turpentine. The lesion was developed without the application of either heat or cold. A central necrotic area is well defined, and there is some evidence of beginning disintegration of the necrotic skin. A surrounding zone of inflammatory reaction is clearly shown.

FIG. 2—The same lesion shown in Figure 1, but 24 hours later, at which time there is relatively little change in the appearance of the surrounding zone of inflammatory reaction, but there is further progress in the disintegration of the necrotic center.

FIG. 3—Actual size color photograph of a lesion 48 hours after the intradermal injection of 0.1 cc turpentine. Immediately after the injection the lesion was kept continuously at a temperature of 40° C. The central necrotic area shows marked evidences of disintegration, and the area of surrounding inflammatory reaction is larger than the field included in the photograph. This surrounding area was much more edematous than in the lesion permitted to develop at body temperature.

FIG. 4—The same lesion shown in Figure 3 but 24 hours after discontinuing the application of heat. There is some diminution in the apparent intensity of the surrounding inflammatory reaction. There is further liquefaction of the central necrotic area.

FIG. 5—Actual size color photograph of a lesion 48 hours after the intradermal injection of 0.1 cc turpentine. Immediately after the injection the lesion was kept continuously at a temperature of 10° C. The central necrotic area is not perceptibly changed in appearance from that immediately after the intradermal injection of turpentine. This area is surrounded by a narrow zone of increased redness which did not appear until more than 24 hours after the injection. There was no visible swelling nor edema. From palpation alone the lesion could not be differentiated from the normal skin.

FIG. 6—The same lesion shown in Figure 5 but 24 hours after discontinuing the application of cold. The central area of necrosis has become clearly differentiated and the surrounding skin shows well developed acute inflammatory reaction. This lesion, which is actually 96 hours old, appears approximately the same as one 24 hours old not subjected to cold or hot applications.

A comparison of Figures 5 and 6 shows not only the marked inhibiting effect of cold on the development of the reaction of living tissues to injury and on the postmortem changes which take place in necrotic tissue but Figure 5 clearly shows the impossibility of determining the extent or even the presence of severe damage to living tissue before the development of any neighborhood response in living tissue or the appearance of postmortem changes in dead tissue.

PLATE I



FIG 1

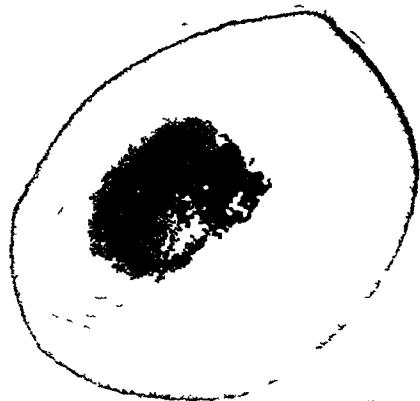


FIG 2

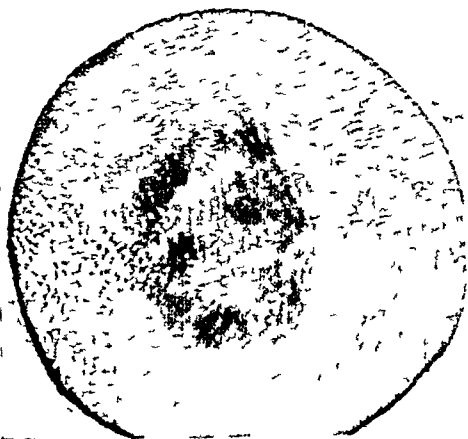


FIG 3

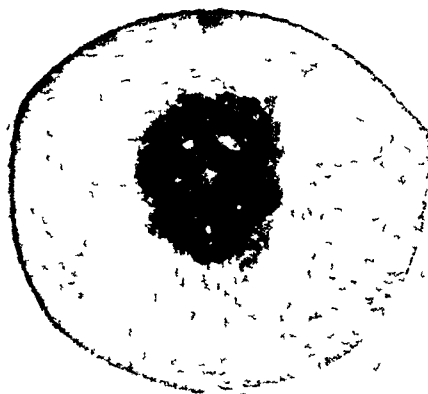


FIG 4

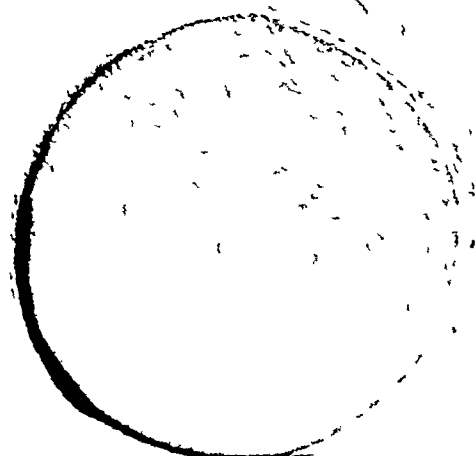


FIG 5

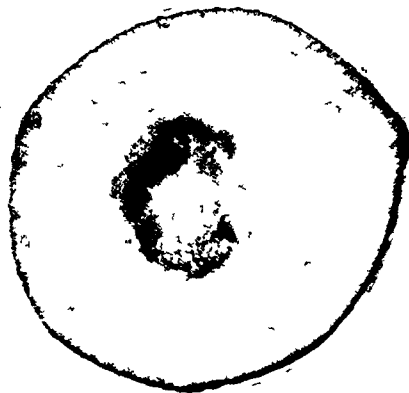


FIG 6

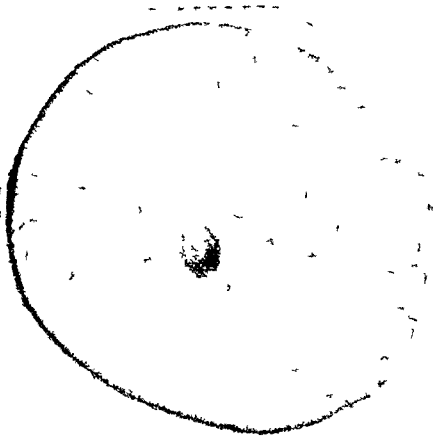


FIG 1

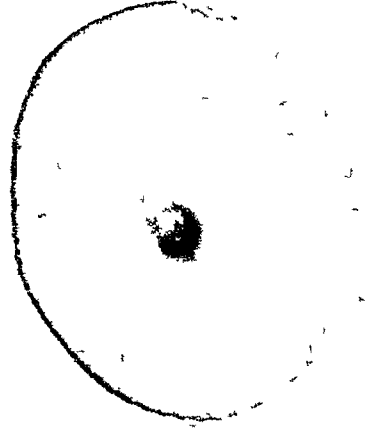


FIG 2

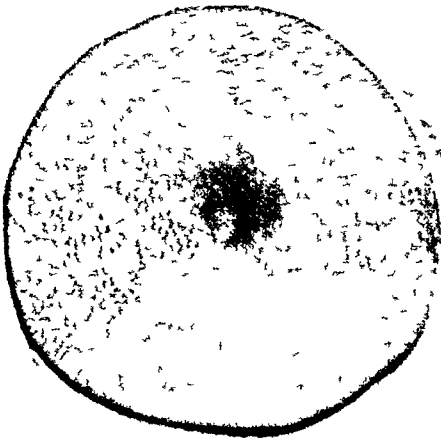


FIG 3

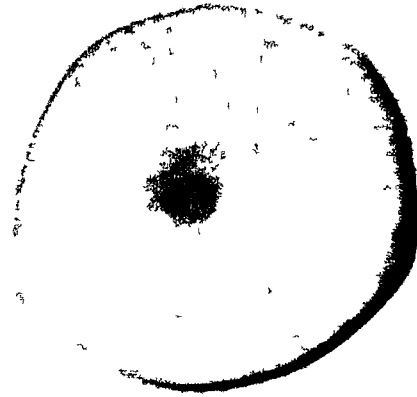


FIG 4

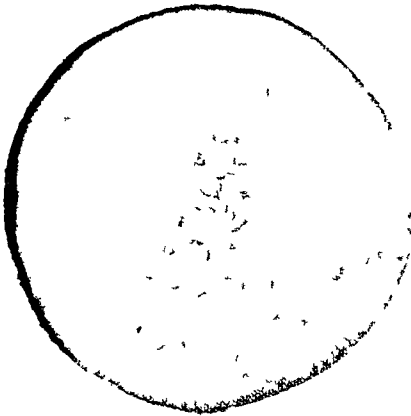


FIG 5

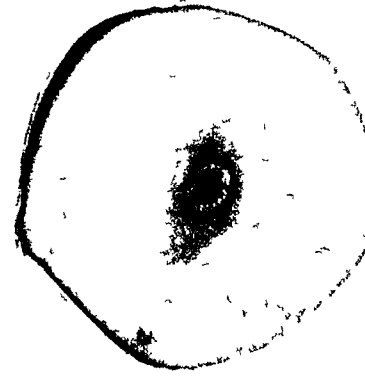


FIG 6

were within a distance of 0.5 cm from a surface which was maintained at a constant temperature by hot and cold applications, it appeared that the depth of change of temperature in the tissues need not be considered as an important influential factor. Evidence that hot or cold applications do not exert an influence to any great depth will be subsequently presented.

Since a previous experimental study² had demonstrated that constant pressure exerts marked influence on living tissues, the size and shape of the bag were arranged so that a minimum pressure would be exerted upon the skin, and each bag was connected with a manometer in order that the pressure exerted upon the skin was equal on each side.

(I) *Results of Experiments in which Aseptic Necrosis was Produced*—In the lesions produced by intradermal injection of oil of turpentine, the area of necrosis in the skin was clearly visible a few minutes after injection, as an opaque yellowish spot approximately one centimeter in diameter. If the temperature of the necrotic area and the surrounding skin is maintained at 40° C, there is at the end of three hours definite induration of the lesion with some swelling of the surrounding skin. At the end of 24 hours there is a marked increase in the amount of swelling of the surrounding skin and a zone of redness occurs around the opaque yellow center. The intensity of the inflammatory reaction at this stage is shown in Plate III, Figure 1. At the end of 48 hours the acute inflammatory process has fully developed in the skin surrounding the lesion, and the necrotic center is beginning to show definite evidence of disintegration by autolysis (Plate I, Fig. 3).

If immediately after the intradermal injection of turpentine, the lesion produced is continuously maintained at a temperature of 10° C, there is at the end of 24 hours no further gross change in the lesion nor in the surrounding

PLATE II, FIG. 1—Actual size color photograph of a lesion 48 hours after the intradermal injection of 0.1 cc of a 24 hour broth culture of *Staphylococcus aureus*. The lesion was developed without the application of either heat or cold. There is an area of necrosis and suppuration with a relatively large area in which there are all the signs of acute inflammatory reaction, most intense nearest the site of injection. The extent and amount of the swelling and edema were more than is evident from the photograph.

FIG. 2—The same lesion as shown in Figure 1, but 24 hours later, in which there is a diminution in the intensity of the inflammatory process in the skin not immediately adjacent to the lesion. There has been further liquefaction of the central necrotic area.

FIG. 3—Actual size color photograph of a lesion 48 hours after the intradermal injection of 0.1 cc of a 24 hour broth culture of *Staphylococcus aureus*. Immediately after the injection the lesion was kept continuously at a temperature of 40° C. There is a well defined central necrotic area which shows definite evidence of softening and suppuration. The surrounding skin shows slightly more swelling and edema than about a lesion permitted to develop at body temperature. The intensity of the redness (partly due to the effect of heat on normal skin) is much greater than about the lesion developed at body temperature.

FIG. 4—The same lesion as shown in Figure 3 but 24 hours after discontinuing the application of heat. Unfortunately, the camera was not accurately focused when the photograph was made but it can be seen that there is diminution in the intensity of the inflammatory reaction on the skin not immediately adjacent to the site of injection. The central necrotic area has undergone further liquefaction until it has become separated from the surrounding living tissues.

FIG. 5—Actual size color photograph of a lesion 48 hours after the intradermal injection of 0.1 cc of a 24 hour broth culture of *Staphylococcus aureus*. Immediately after the injection the lesion was kept continuously at a temperature of 10° C. The only change which is shown in the skin at the site of the injection is a small area of bluish discoloration. (Note: The small red spots in the surrounding skin shown in the photograph are produced by the shaving of the animal's hair previous to injection). From palpation alone it was impossible to locate the site of the injection. There was no visible redness or edema. This shows that low temperature will inhibit the development of those conditions which usually make it possible to determine the extent and magnitude of damage to tissues.

FIG. 6—The same lesion as shown in Figure 5 but 24 hours after discontinuing the application of cold three hours after which the manifestations of an acute inflammatory process appeared in the skin surrounding the site of injection. Twenty-four hours after removal of the cold applications the central necrotic area is clearly differentiated. It is interesting and perhaps important that this necrotic area was in most instances considerably larger than those in similar lesions developing at body temperature.

skin, and a microscopic section shows no evidence of edema nor of leukocyte infiltration (Plate III, Fig 2) At the end of 48 hours there is still no induration nor visible swelling There is at this time only a narrow red zone surrounding the area of necrosis (Plate I, Fig 5)

If the temperature of the area of necrosis produced by intradermal injection of turpentine is not altered by external application of either heat or cold, the intensity of the inflammatory process is distinctly less during any period short of 48 hours than about a lesion in the same period but which has been maintained at 40° C (Plate I, Fig 1) The difference between the lesion maintained at 37° C, and the one at 40° C is less than that between the lesion at body temperature and one maintained at 10° C, and the differences are such as to suggest that if there were some method of measurement of rate of development of an acute inflammatory process, it would be proportionate arithmetically rather than geometrically to temperature in the range of 0° to 40° C

(II) *Experiments in Which the Staphylococcus Aureus Was Injected Intradermally*—The lesions produced by intradermal injection of the standardized strain of *Staphylococcus aureus* which were not subjected to the influence of hot or cold applications were remarkably constant in size, shape, extent of necrosis and rate of development The lesion 48 hours after injection is shown in Plate II, Figure 1

If the site of the intradermal injection of *Staphylococcus aureus* is maintained at 40° C, the physical changes of the inflammatory process develop more rapidly and are of greater magnitude and intensity At 24 hours there is marked swelling, redness and induration about the lesion, and microscopic examination shows the characteristic picture of an acute suppurative inflammation (Plate III, Fig 3) At 48 hours there is a central area of necrosis, softening, ulceration and a purulent discharge (Plate II, Fig 3)

If the site of inoculation of *Staphylococcus aureus* is maintained at 10° C, there is at 24 hours a small area of slight discoloration (ecchymosis) about the puncture, and no visible change in the surrounding skin Microscopic examination shows only an occasional extravascular leukocyte near the tract of the needle (Plate III, Fig 2) It is interesting that there is more evidence of inflammation in the deep subcutaneous tissues in which there has been less reduction of the temperature At 48 hours the discoloration of the skin immediately adjacent to the puncture is increased in intensity and slightly in extent and microscopic examination shows an increase in the number of extravascular leukocytes, but there is no evidence of edema and no evidence of necrosis The gross characteristics of this lesion at 48 hours are shown in Plate II, Figure 5

(III) *Changes in Experimental Lesions after Cessation of Hot and Cold Applications*—It is important to call attention to the fact that any observation of a condition existing in a wound is only significant when it is related to past or future developments A recent wound is in reality a combination and a mixture of many influential factors The magnitude or even the presence in

FIG 1



FIG 2



FIG 3



FIG 4

FIG 1.—Photomicrograph of a lesion 24 hours after the intradermal injection of 0.1 cc turpentine. Immediately after the injection the lesion was kept continuously at a temperature of 40° C. The existence of a marked acute inflammatory reaction is shown by the presence of edema and a large number of extravascular polymorphonuclear leukocytes.

FIG 2.—Photomicrograph of a lesion 24 hours after the intradermal injection of 0.1 cc turpentine. Immediately after the injection the lesion was kept continuously at a temperature of 10° C. Microscopic section shows no evidence of inflammation or necrosis.

FIG 3.—Photomicrograph of a lesion 24 hours after the intradermal injection of 0.1 cc of a 24 hour broth culture of *Staphylococcus aureus*. Immediately after the injection the lesion was kept at a temperature of 40° C. The section shows the characteristic microscopic picture of a severe acute inflammatory reaction. At the top of the illustration ulceration and the presence of purulent exudate are clearly visible.

FIG 4.—Photomicrograph of a lesion 24 hours after the intradermal injection of 0.1 cc of a 24 hour broth culture of *Staphylococcus aureus*. Immediately after the injection the lesion was kept continuously at a temperature of 10° C. The section shows no evidence of necrosis nor inflammatory reaction in the tissue nearest the surface to which cold was applied. The entire thickness of the skin appears quite normal. At the bottom of the illustration there is a definite infiltration of the subcutaneous fat by polymorphonuclear leukocytes. This figure clearly illustrates the marked influence which cold exerts upon the development of a tissue response to bacterial invasion. It also shows very clearly the relatively small depth of the influence exerted by the application of cold to the surface of a living healthy animal with a normal circulation.

large amount or the total absence of two of the most important of these influential factors, namely, injury to tissues and contamination with pathogenic organisms, can be determined only by future developments. From the examination of a microscopic section one could not testify as to whether the bloc of tissue from which the section was cut came from a living or dead body, nor whether it was killed before or after separation from the body. Likewise, a bloc of necrotic tissue in a living animal is subject to the same postmortem changes as would occur anywhere else with the same environmental conditions of temperature, moisture and bacterial contamination.

Experimental lesions produced by intradermal injections of *Staphylococcus aureus* and turpentine and subjected to both hot and cold applications were observed for varying periods after cessation of the hot or cold applications. The changes occurring in and about the experimental lesions during a period of 24 hours after discontinuing the applications of heat or cold were considered as the most reliable evidence for interpreting conditions existent at the time of removal of hot or cold applications. This period is long enough at a temperature of 37° C for necrotic tissues to show obvious postmortem changes and for living tissues at body temperature to develop unmistakable signs of a response to injury. Some of the changes occurring during this period are evident from a comparison of the photographs reproduced in Plates I and II.

Plate I, Figure 5 is a photograph of the lesion produced by intradermal injection of 0.1 cc turpentine to which cold has been applied for 48 hours. During this period there has been no demonstrable change in the central area and only very slight change in the surrounding skin, which is in sharp contrast to the marked changes which have occurred in and about the same lesion maintained at body temperature and shown in Plate I, Figure 1. Without any knowledge of subsequent developments, but with the information which could be obtained from the use of all available methods of examination of these experimental lesions as they exist at the end of 48 hours after their development at different temperatures, it would be difficult to avoid the conclusion that cold applications are an effective method of preventing undesirable consequences of intradermal injections of turpentine. Subsequent changes after removal of cold show that this conclusion is incorrect.

If cold applications to the experimental lesion produced by turpentine, and shown in Plate I, Figure 5, are discontinued at the end of 48 hours, the characteristic signs of an inflammatory reaction in the surrounding skin begin to appear in two or three hours. The central area becomes more discolored and definite signs of postmortem decomposition develop, and 24 hours after discontinuance of the cold application the lesion, which is now 96 hours old, is approximately the same as a similarly produced lesion developing at body temperature for 24 hours. Since lowering of the temperature of the skin after the injection of turpentine could hardly influence the time at which necrosis took place or the amount of tissue which was killed, the influence must have been one of inhibition of postmortem change in the necrotic tissue and of the inflammatory process in the adjacent living structures. Whether the reaction

in the adjacent structures is absent because of the inhibition of the tissue's normal response to a chemical poison (turpentine) or because of the inhibition of the production of toxin by autolysis of the necrotic tissue, is not known. This should be determined by a comparative study of the influence of cold applications in a similar manner to an area of necrosis produced by some method in which a necrotizing agent would not remain in the tissues, *e g*, coagulation by heat or freezing.

If experimental lesions produced by *Staphylococcus aureus* and maintained at temperatures above or below body temperature for 48 hours are observed for an additional period of 24 hours after removal of hot or cold applications, the changes which occur are illustrated in Plate II. The discontinuance of hot applications is followed by a diminution in the intensity of the redness of the surrounding tissues, but otherwise there are no more changes taking place than there are in a lesion subjected to neither hot nor cold applications. The lesion which has been subjected to cold applications for 48 hours, and which at this time is a small area in which there is only ecchymosis with no evidence of reaction in the adjacent tissue, begins in two to three hours after the removal of the cold application to be transformed into a lesion with a sharply differentiated central area of distintegrating dead tissue, surrounded by tissues showing the characteristics of acute inflammation. At the end of 24 hours the lesion does not differ in gross appearance from one developing at body temperature, except that it usually shows a slightly larger necrotic center.

Although these experiments demonstrate conclusively that temperature exerts a marked influence on the development of the inflammatory process and on the postmortem changes in necrotic tissue, no experiments were performed for the purpose of study of any influence temperature might exert on an inflammatory reaction which had already developed. The experimental lesions were the most superficial which could be produced and were, therefore, in structures whose temperature could be most influenced by external applications. The appearance of some reactive changes in the subcutaneous tissues indicated the relatively small depth of temperature alteration by the external applications. The impossibility of cooling the deeper structures, which are constantly being perfused by warm blood, is obvious. Furthermore, it is quite possible that cooling of the superficial tissues might operate to stimulate a more rapid development of reaction in the deeper structures in which there might be, because of a more abundant circulation, actually an increase in temperature.

Although the experiments in which the experimental lesion was produced by inoculation with staphylococcus were markedly influenced by changes in temperature, the mechanism of this influence was not determined. Whether the stimulus for the reaction was less because of inhibition of bacterial growth or diffusions of toxins, or whether there was an inhibition of reaction of the tissue, is not known. It is interesting that the area of necrosis which subsequently appeared after cold application was larger than if the lesion developed at body temperature.

It is also worth while to point out a possible bearing these experiments may have on the pathogenesis and treatment of surgical shock. Reduction of the temperature of the tissues certainly exercises a marked effect on the exudation of fluids into tissues and on the disintegration of devitalized tissues, so that no matter which of the two most generally accepted theories of shock is accepted, it would appear that the results obtained in these experiments do not support the generally accepted use of the application of external heat for the prevention or treatment of surgical shock. In surgical shock the temperature of the cold, bloodless extremities would be more influenced, *en masse*, than extremities with an abundant circulation.

These experiments at least suggest that there is reasonable doubt of the wisdom of inhibiting an inflammatory reaction by cold application or of the universal application of heat to the extremities of a patient in surgical shock. After all, these conditions are natural responses, and efforts to reverse normal physiologic processes bring to mind the now universally discarded fever reducing drugs of the past.

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REGENERATION OF EPIPHYSEAL CARTILAGE*

AN EXPERIMENTAL STUDY

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THESE EXPERIMENTS were undertaken to determine the extent to which an epiphysis or epiphyseal growth cartilage may regenerate when either one or both has been partially or completely destroyed. That longitudinal growth of the shaft of bones which are preformed in cartilage occurs only from the anatomically intact epiphyseal cartilage plate has been accepted as a fact.

Selye¹ conducted experiments, the results of which he interpreted as reflecting some doubt on the complete accuracy of this theory. He performed mid thigh amputations on rats 12 to 15 days old and at necropsy, 19 to 25 days later, found a layer of cartilage which closed the amputation end of the bone, and assumed this to be a growth cartilage. He did not state that it might have been cartilage of the callus repairing the cut end of the bony stump. Selye concluded, without demonstrating evidence adequate to support his theories, that "the growth of very young bones is largely independent both of the pituitary growth hormone and of the derivatives of the epiphyseal cartilage anlage." We also have attempted to either confirm or refute this hypothesis.

Methods and Materials—Two distinct sets of experiments were performed, one on white rats and the other on rabbits. Sixty-one animals, 15 days old, were used in the rat experiments. The distal end of the left femur was exposed under ether anesthesia by reflecting the patella tendon, without stripping periosteum from the diaphysis. Table I shows the procedures that were then carried out.

TABLE I

Group	Number of Rats
A Midfemoral amputation	25
B Subtotal resection of lateral half of distal femoral epiphysis leaving the cartilage plate	13
C Subtotal resection of distal femoral epiphysis leaving the cartilage plate	13
D Resection of medial half of distal femoral epiphyseal cartilage plate	5
E Complete resection of distal femoral epiphyseal cartilage plate	5
Total	61

From Group A, one rat was sacrificed every second day from the seventh to the thirty-fifth postoperative day and the remaining ten rats at nine

* This study was aided by a grant from the Douglas Smith Foundation for Medical Research

weeks One rat in each of Groups B, C, D, and E was sacrificed at four weeks and the remaining rats at the end of nine weeks

Results—Group A—Midfemoral Amputation The healing process was concerned primarily with the repair of the defect at the end of the bone, and was not influenced by the angle of the resection as related to the long axis of the femur After seven days, a fibrous cap containing areas of fibrocartilage cells closed the amputation end of the shaft After 15 days this fibrous cap had increased in thickness, and was microscopically similar to the callus of a healing fracture, containing fibrous tissue, osteoid tissue, cartilage, and

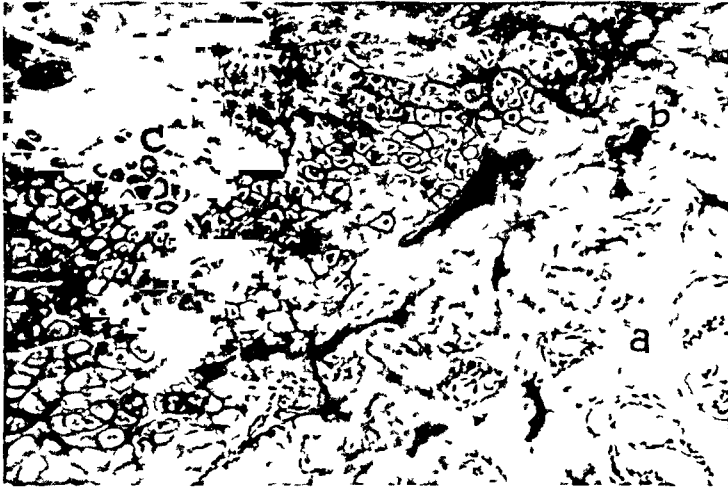


FIG 1—Photomicrograph of an amputation stump 30 days after operation showing a callus typical of a healing fracture of a young bone which is preformed in cartilage The elements from the surface inward are (c) cartilage, (b) ossifying zone, (a) bone (X240)

areas of calcification and ossification The predominance of proliferating cartilage cells in the callus across the end of the shaft of some of the later specimen was striking (Fig 1) We may reasonably assume that what Selye regarded as a regenerated longitudinal growth disk was this cartilage of the callus of repair No length growth occurred from this tissue in the rats of our experiments The complete microscopic analysis could leave no doubt that this cartilage was structurally and genetically identical with that which is commonly found in the callus of healing fractures in extremely young animals, or repair of defects of bones which are preformed in cartilage Organization of the callus into mature bone was complete in four rats examined from the twenty-ninth to the thirty-fifth day After a period of nine weeks, there was bony repair of all of the stumps, some of which were rounded and some conical

Groups B and C—Subtotal Resection of Epiphyses In these experiments, the lower femoral epiphysis was exposed anteriorly after lateral reflection of the tibiopatella tendon In Group B, the lateral half of the epiphysis was cut straight across distal to the wavy epiphyseal line leaving behind a small amount of bone that was greatest along the outer aspect In Group C, the epiphysis was cut completely across, leaving small amounts

of bone at the edges and in the intermediary notch. Resected portions of the epiphysis, including the articular cartilage, were not restored except for a small amount of proliferation of the bone that was left behind with the formation of a bony cortex. The defects were repaired, in part, by dense

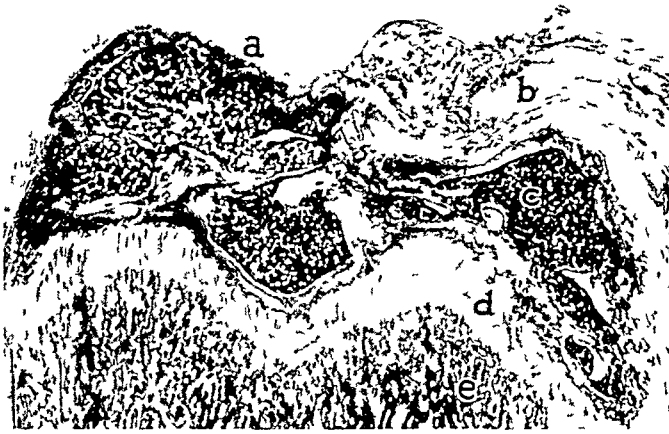


FIG. 2.—Photomicrograph of the distal end of a rat femur nine weeks following subtotal hemiexcision of the epiphysis. It shows fibrous tissue repair (b), some proliferation of bone of the ossification center (c), but no regeneration of the hyaline articular cartilage locally or by overgrowth from the unresected half of the epiphysis (a). The epiphyseal plate (d) is intact with normal longitudinal growth of the metaphysis (e).

fibrous tissue. In most cases of hemiexcision there was overgrowth by this fibrous tissue with partial absorption of the articular cartilage of the remaining condyle. The joint space was obliterated by fibrous adhesions. Longitudinal growth of the diaphysis continued, providing the epiphyseal plate was not disturbed at operation (Figs 2 and 3).

Group D—Hemiexcision of the Epiphyseal Cartilage Plate. When the medial portion of the cartilage plate was excised, a bony bridge formed between epiphysis and diaphysis and growth on this side was arrested while longitudinal growth continued on the lateral side for a time. This resulted in an increasing deformity, characterized by tilting of the condyles of the femur, until the plane of the articular surfaces formed an acute angle with the long axis of the shaft, creating limb shortening and a marked varus deformity of the knee (Fig. 4 E).

Group E—Resection of the entire epiphyseal plate including thin sections of bony metaphysis and epiphysis produced immediate arrestment of longitudinal growth from this end of the femur. In four experiments there was bony union of the epiphysis and shaft, while in one nine-weeks experiment the epiphysis was ununited and markedly displaced on the shaft (Fig. 4 D). The four femurs from which the junction cartilage was removed, were only about two-thirds as long as the normal controls at the end of nine weeks.

A second group of experiments (Table II) was performed upon 20 rabbits, three days old. They were sacrificed in from six weeks to seven months after operation.

EPIPHYSEAL CARTILAGE

TABLE II

Group	Number of Rabbits (3 days old)
A Cartilaginous head of the right femur was excised down to the epiphyseal plate	4
B The entire head and part of the neck of the right femur were excised	4
C The proximal one third of the shaft of the femur including the head and both trochanters was excised	4
D The external capsule of the right hip was cut completely around and the ligamentum teres was divided	4
E The external capsule of the right hip was cut all the way around the ligamentum teres was divided and the synovial reflection on the neck was circumcised and stripped down to the intertrochanteric line	4
Total	20

Results—The results of these experiments were similar to those in which young rats were used

Group A—Resection of the cartilaginous head of the right femur, without injury to the epiphyseal line, did not interfere with longitudinal growth of the neck or of the shaft of the femur and the epiphysis did not regenerate

Group B—After excision of the head and part of the neck of the right femur, the trochanter and shaft dislocated upward Subsequent roentgeno-



FIG 3—Photomicrograph of the distal end of rat femur nine weeks after subtotal resection of the epiphysis, showing fibrous tissue of repair (a) but no regeneration of articular cartilage Normal longitudinal growth of metaphysis (c) is occurring through intact epiphyseal plate (d) (×30)

graphic and gross and histologic studies failed to reveal any evidence of regeneration of the head or of the resected portion of the neck At necropsy, the proximal end of the neck was found to have healed over with dense fibrous tissue The neck failed to develop, but longitudinal growth of the femoral shaft continued from the greater trochanter In one experiment, 56 days after operation, the distance from the tip of the greater trochanter to

the intercondylar notch of the femur showed shortening of only 2 Mm (Fig 5 A), as compared to the opposite side

Group C—Excision of the proximal third of the shaft of the femur, including the head, neck, and both trochanters, produced almost complete loss of function in the extremity. However, the distal two-thirds of the

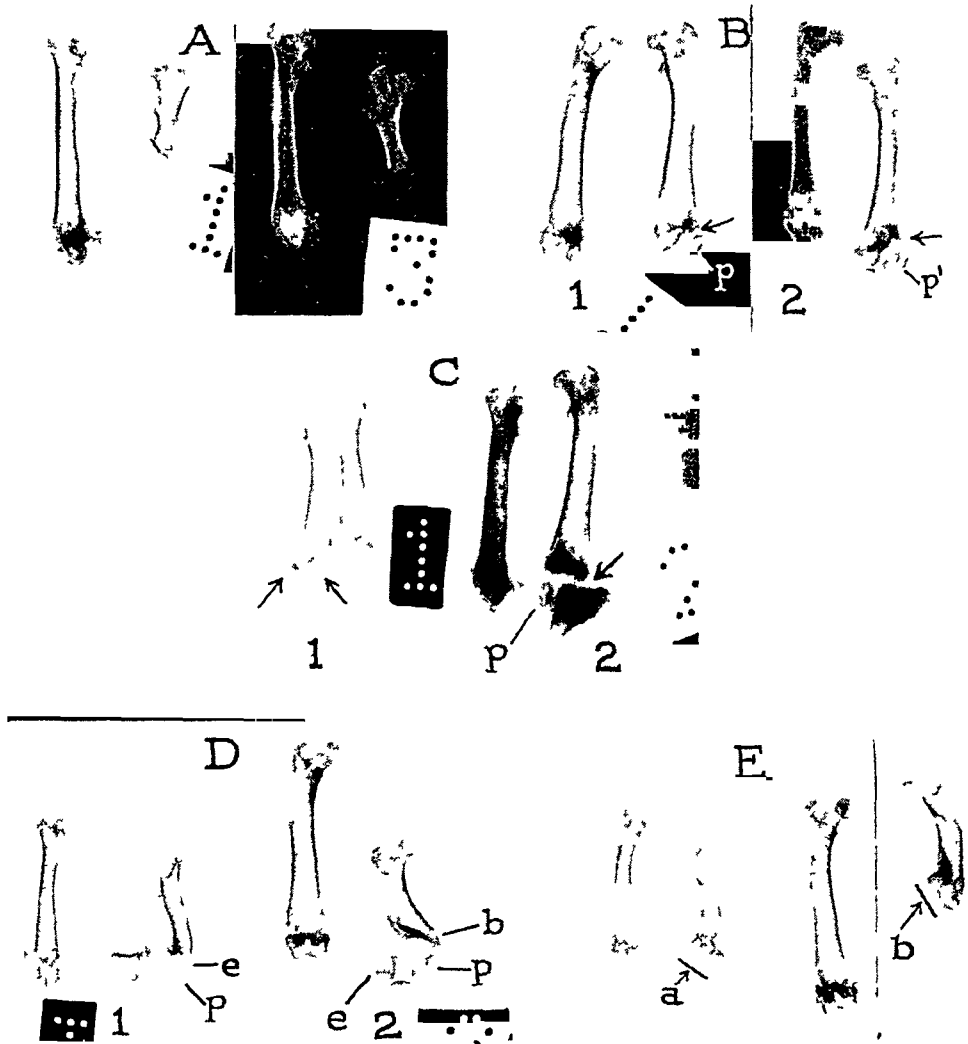


FIG 4—A Roentgenograms of rat femurs showing repair of amputation stumps nine weeks after operation. The markers (small sections of hypodermic needle stylets) indicate that no longitudinal growth has occurred from the fibrocartilaginous cap which formed early over the resected end of the femur.

B Roentgenograms showing the defect resulting from lateral subtotal hemic excision of the distal femoral epiphysis nine weeks after operation, with the shadow of the patella (p) partly overlying same. The notch on the lateral side of the metaphysis of Rat 2 resulted from surgical trauma to the epiphyseal plate.

C Illustrates the result of subtotal excision of the distal femoral epiphysis. In Rat 1 (four weeks) and in Rat 2 (nine weeks after operation) there has been no shortening of the diaphyses, but the epiphyses show no evidence of regeneration. Patella of Rat 2 is indicated (p).

D Complete excision of the distal femoral epiphyseal plate resulted in growth arrest and marked shortening. After four weeks (Rat 1) the epiphysis (e) was fused to the diaphysis. A faint shadow of the patella (p) may be noted. In Rat 2 after nine weeks the epiphysis remained ununited and the end of the shaft healed with well formed bone (b).

E Rat femurs showing deformity (a) four weeks (b) nine weeks after excision of the mesial portion of the distal epiphyseal plate. The condyles are tilted obliquely and there is marked shortening due to immediate growth arrest from the medial, and later, but still prematurely obliteration of the lateral portion of the growth disk.

femur developed in length and breadth to a surprising degree, approximating that of the normal. In one experiment, after five months (Fig 5 B), the diameter of the shaft in the distal one-third of the femur was essentially the same as that of the control side and the condyles of the femur were well developed. The proximal end of the shaft of the femur was found to have healed over with well-organized bone, resembling a conical amputation stump.

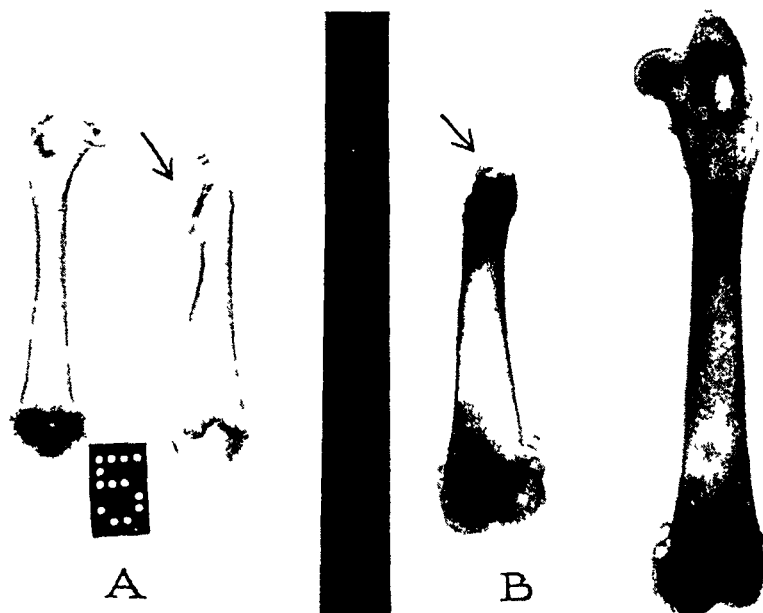


FIG 5—A Roentgenograms of the control and operated femurs of a rabbit 56 days after excision of the head and proximal portion of the neck of the femur. There has been no regeneration of the capital femoral epiphysis. Longitudinal growth of the shaft has continued from the greater trochanter epiphysis, but there has been a loss of two Mm. in length, as compared with the control.

B Six months after excision of the proximal one-third of the femur, including the head and both trochanteric epiphyses, the amputated end of the femur has healed across with well-organized bone. The condyles of the femur and the distal one-third of the shaft have developed to approximately a normal extent, but no longitudinal growth occurred from the cartilage of repair and no epiphysis was regenerated.

Group D—When the capsule of the right hip joint was cut completely around and the ligamentum teres divided, no definite interference with the growth of the head and neck of the femur could be demonstrated. These dislocated upward, but the femur continued to grow at a rate comparable to that of the control side (Fig 6 A).

Group E—When, in addition to cutting the capsule all the way around and dividing the ligamentum teres, synovia and capsular attachments were stripped from the metaphysis, *i.e.*, neck, down to the intertrochanteric line, gross deformity occurred. This was characterized by flattening of the head with shortening of the neck and what, roentgenographically, appeared to be bone absorption in the neck. After 46 days, the tip of the greater trochanter was found to be above the level of the acetabulum, the mesial side of the neck shortened, and there was marked coxa vara (Fig 6 B). The appearance of this femoral head and neck is similar to Legg-Calve-Perthes' disease and is indicative of aseptic bone necrosis.

Discussion—The results of these experiments may be interpreted as refutation of the conclusions of Selye with regard to the regeneration of a functioning cartilage plate which might contribute to the longitudinal growth of the bone following amputation in very young animals. There was bony closure of the medullary cavity of the resected end, which became rounded

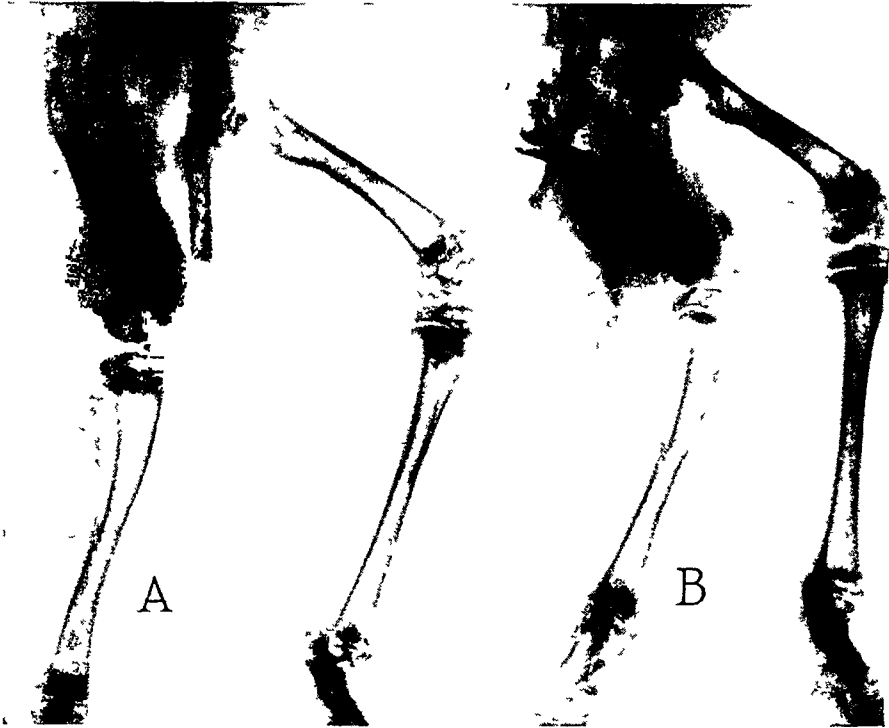


FIG 6—A Roentgenograms of pelvis and lower extremities of a rabbit 46 days after sectioning the capsule of the hip joint and division of the ligamentum teres. The hip was dislocated upward, but the two femurs are the same length. The head and neck of the femur have continued to grow and have maintained a normal relationship with the shaft.

B Roentgenogram of a rabbit 46 days after section of the capsule and ligamentum teres and extensive stripping of synovia and soft tissue attachments from the neck to the intertrochanteric line. The flattened head, shortened neck, and areas of absorption in the metaphysis suggest Legg Calve Perthes disease indicative of aseptic bone necrosis.

or conical in contour. The remaining shaft did increase in length by growth from the other end, and Mullen and Gatewood² have shown that overgrowth may even occur at that epiphyseal line.

These studies further indicate that excision of the epiphysis, including the articular cartilage, but without trauma to the epiphyseal cartilage plate, is followed by slight bony regeneration, but no articular cartilage and there is no further longitudinal growth of the epiphysis. However, it causes no disturbance of longitudinal growth of the diaphysis.

This is evidence, although incomplete, which adds confirmation to the hypotheses of Nussbaum,³ Peyton,⁴ and Siegling,⁵ that the articular cartilage serves as a longitudinal growth cartilage for the epiphysis and is to the epiphysis what the epiphyseal junction cartilage is to the diaphysis. Since the articular surface is covered by hyaline cartilage, these results conform to the generally accepted theory which is to the effect that hyaline cartilage,

destroyed, does not regenerate, but is replaced by fibrous connective tissue or fibrocartilage, neither of which can function as centers of growth

Haas⁶ demonstrated that it is possible to curette out the ossification center of an epiphysis without seriously affecting either the growth of the shaft or of the epiphysis and in such cases this center of ossification reforms

Banks, Krigsten, and Compeire⁷ have recently reported the regeneration of epiphyseal ossification centers in young children following their destruction by pyogenic (four cases) or tuberculous (one case) infection, but in whom there had been preservation of varying amounts of their cartilaginous portions. In each case, longitudinal growth of the shaft continued, and indicated the remarkable degree of preservation of the growth cartilage disk in the presence of extensive infection within the epiphysis itself

Loss of any portion, however, of the epiphyseal cartilage plate from injury results in partial to complete growth arrest with the development of deformity and shortening of the involved extremity. If only a portion of the plate is experimentally removed, a bony bridge forms, producing prompt growth arrest at this point with gradually decreasing activity of the remaining untraumatized junction cartilage, until it, too, undergoes premature fusion. In each instance in which the epiphyseal plate was the focus of surgical attack, it was definitely shown, confirming previous reports by Haas, that this epiphyseal cartilage plate possesses no capacity for regeneration

CONCLUSIONS

(1) An epiphysis which, microscopically, contains the elements of a growth cartilage plate and which has the power to contribute to the longitudinal growth of bones is not regenerated after complete excision in very young rats or rabbits. Cartilage forms in the repair of the end of the stump, but disappears when the repair is complete

(2) The entire longitudinal growth of the remaining segment of a long bone after excision of one end, as in the case of amputation, occurs entirely from the remaining epiphysis at the other end

(3) Subtotal resection of all or one-half of the epiphysis is followed by slight regeneration of the bony center, but no regeneration of epiphyseal or articular cartilage and there is arrest of longitudinal growth of that portion of the epiphysis

(4) Following injury or resection of the epiphyseal cartilage plate, the longitudinal growth of the shaft is either partly or completely arrested. If completely arrested, epiphyseodesis is established

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INFUSIONS OF BLOOD AND OTHER FLUIDS VIA THE BONE MARROW IN TRAUMATIC SHOCK AND OTHER FORMS OF PERIPHERAL CIRCULATORY FAILURE *

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IN FAILURE of the peripheral circulation resulting from various causes, the administration of plasma or blood is often of great benefit. When the circulatory depression is marked and of some standing it is difficult to introduce any substances into the circulation by the venous route. Several factors operate to create this difficulty. The diminution in blood flow, which in certain vessels almost amounts to stagnation, renders it difficult to bring out the peripheral veins by the usual methods. The peripheral veins themselves are collapsed because of the reduced blood volume and poor venous return. If venesection is attempted, it is sometimes, even then, not possible to enter the veins, the walls of which may be in close apposition. Even when the vein is entered, one may not be able to inject fluid rapidly, the sluggish column of blood ahead prevents a rapid drainage of injected material with the result that further forceful injection may lead, especially in children, to a "blowing out" of the vein at the puncture site. All these difficulties which are the result of peripheral circulatory failure also interfere with any attempts at re-establishing the level of the blood volume, thereby helping to perpetuate the vicious circle. Attempts to re-establish blood volume other than by the *direct* introduction of fluids into the circulation fail, because of the markedly slow absorption of such fluids by the tissues, under these abnormal conditions.

During a stage when fluids are most urgently needed, one is left without ready access to the central portion of the circulation. It has occurred to us that, under such conditions, the bone marrow offers the ideal site for the introduction of fluids until the patient has reached such a stage that the peripheral circulation is restored and access to the veins is again possible. Since the marrow veins are surrounded by a rigid envelope, they are less likely to collapse, and can probably withstand forcible injection without overdilatation and leakage better than the poorly supported peripheral veins.

Substances injected into the bone marrow cavity are taken up immedi-

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ately into the venous circulation apparently unchanged¹ This method for giving fluids has been used in 72 patients to date, without any local or constitutional reactions^{2 3} Experience with the method in animals having failure of the peripheral circulation due to hemorrhage³ or in those undergoing an insulin reaction¹ impressed us with the desirability of widening the application of this method to the commonly encountered states of acute peripheral circulatory failure as observed in the operating room, in obstetric practice, in accidents, in industrial life or on the battlefield Since our experience is limited to such incidents as are encountered in general hospital practice, this report is intended to draw the attention of those in whose hands the method may find a greater application

FATE OF COLORED SOLUTIONS INJECTED INTO THE MARROW CAVITY OF THE STERNUM—If 10 cc of green vinylite solution (a plastic material which solidifies on exposure to the air) are injected into the manubrium of the intact cadaver of an adult man, the solution leaves the marrow at once, enters the internal mammary veins and most of it is found in the form of a rubbery mass in the right auricle The accompanying figure (Fig 1b) illustrates the path traversed by the solution after it is injected into the sternum Injection of dyes into a cadaver can give only an approximate idea of their spread during life, because of the absence of the circulation The quick appearance of the dye in the auricle, however, serves to demonstrate the comparatively short distance between the sternal marrow and the right side of the heart Rapid introduction of fluid into this side of the heart, therefore, may help to restore cardiac output during acute peripheral circulatory failure, by increasing the volume of blood returning to the central portion of the circulation

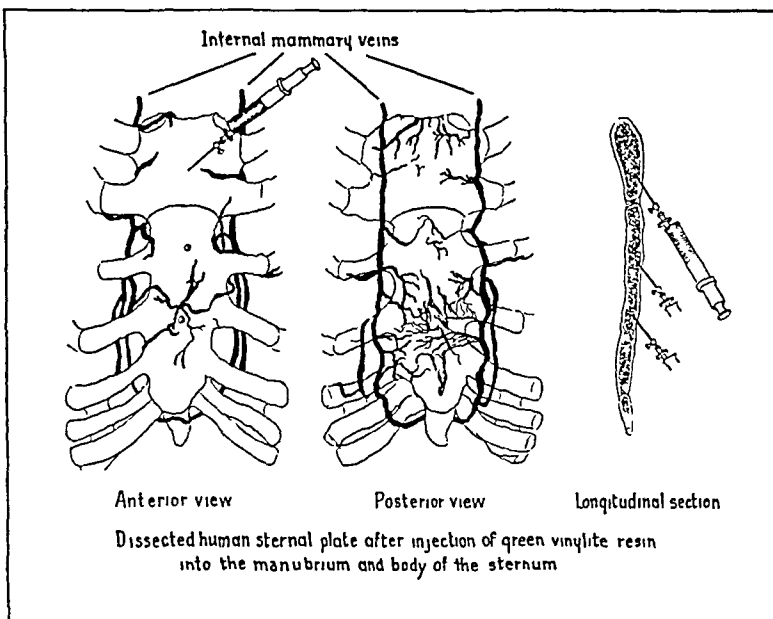


FIG 1a (For Fig 1b and legends see opposite page) →

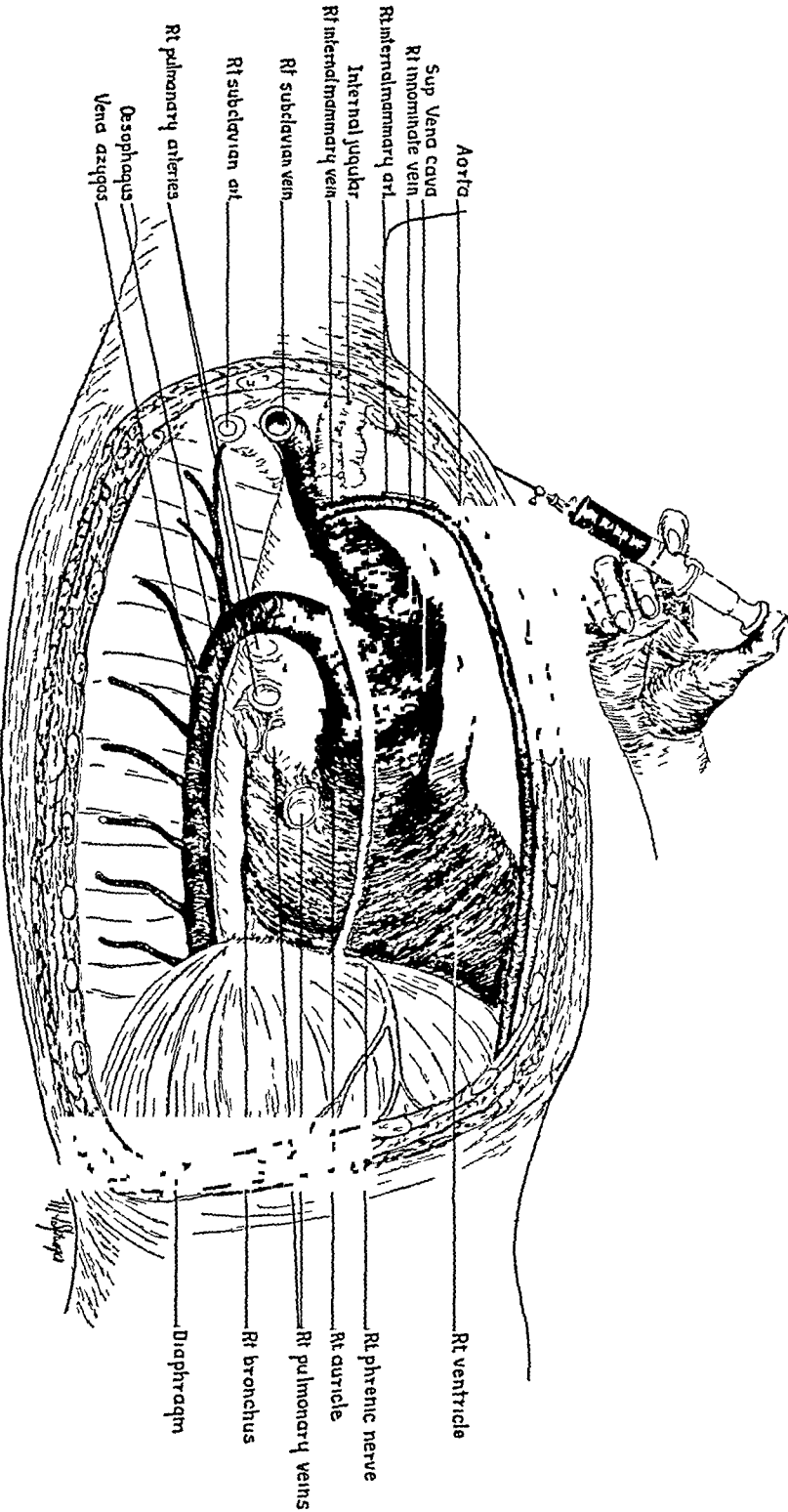


Fig 1b

Fig 1b—Right parasternal section of the thorax of an adult man (right lung removed). The path traversed by a green dyed solution injected into the sternal marrow cavity is indicated by the shaded vessels. Note the filling out of the vena azygos and intercostal veins, a result perhaps of the lack of resistance offered after death by the blood in that vein, and the absence of the sucking action of the right auricle.

Figure 1a (see illustration opposite page) illustrates the distribution of the dye in the retrosternal veins and the location of the needles during the injection.

Technic—Details of the technic for introducing fluids into the sternal marrow have been described at length elsewhere^{2 3} Only such variations in technic that may be applicable in patients with peripheral circulatory failure will be mentioned here

After the needle has been introduced into the sternum (or tibia) and marrow has been obtained by aspiration, the syringe containing the material to be administered is inserted into the needle and the material is injected as fast as the resistance offered to it will allow In conscious adult patients, rates of injection over 20 cc a minute are usually accompanied by an unpleasant feeling of fulness in the sternum which passes off immediately after cessa-

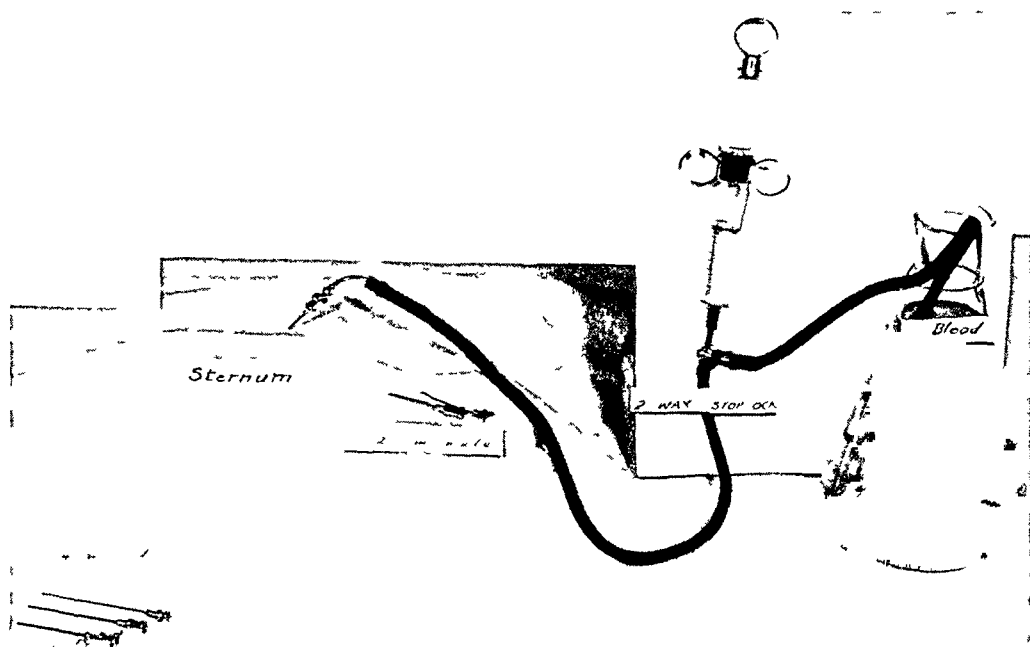


FIG 2—Arrangement for the rapid injection of fluids into the bone marrow The blood may be put in a burette or inverted flask held above the level of the syringe thus making easier to aspirate blood into it All connections must be tight A set such as the above including two complete marrow infusion needles (4 and 2.5 cm long respectively) sterilized, may be held in readiness in the central hospital sterilizing rooms or in emergency stations for use at once when needed

tion of the injection If it is contemplated to inject more than 50 cc of fluid, much time may be saved by using a manually operated two-way stopcock with two thin-walled rubber tubes, one leading into the needle by means of an adapter and the other tube leading into the reservoir holding the blood, plasma or whatever fluid is to be injected (Fig 2) By this means, it becomes unnecessary to remove the syringe from the sternal needle every time it has to be filled If it is felt that a more rapid rate of injection is desirable than that obtained by using a single needle, two needles may be inserted at once in the sternum, one in the manubrium (above the angle of Louis) and the other 5 cm below it, in the body of the sternum Since the marrow cavity of the manubrium and the body of the sternum seldom communicate, it is possible to inject material through an orifice in the manubrium without its coming out of another orifice made in the body of the same bone Care should be taken,

however, not to have both offices made in the same portion of the sternum unless the fluid is going in with the same pressure through both of them. After the injection of the fluid is completed, the needle may be connected with a standard gravity infusion apparatus. If the patient has reacted from the state of collapse and the blood pressure has risen to a normal level, it may then be possible to use the peripheral veins.

The following cases illustrate the type of acute emergency in which this method finds its greatest usefulness.

Case 1 — (From the service of Dr. George J. Boines, Wilmington General Hospital, Wilmington, Del.) R. S., a white girl, age nine, had her tonsils removed on August 26, 1941, and went home the following day, apparently in good condition. On August 30, about 10 P. M., she began to vomit large amounts of blood and a few clots. During that day the child had been unable to eat anything because of pain in the throat. When admitted to the hospital she was having some bleeding in the postnasal space where a few large clots were observed. After the clots were removed, it was seen that the bleeding came from the posterior pharyngeal wall and was apparently controlled by packing. During the night the child began to bleed again and vomited many clots. Packing was again resorted to and seemed to control the bleeding. At 2:30 A. M. the child's condition became worse. She was cold, pale, and her skin was clammy. Her pulse was 170, weak and thready and her respirations 48. Stimulation was given and an attempt was made to give fluids intravenously but the veins of both arms and legs were collapsed and it was not possible to distend them by the usual methods. When, after repeated trials, it was felt that it was impossible to introduce a needle into any of the veins, the blood was given through the sternum using a marrow infusion needle. After aspirating a slight amount of blood from the sternum, the donor's blood was given through the needle. Three hundred cubic centimeters of citrated blood were infused followed by 200 cc. of normal saline solution, in two hours and 50 minutes. At 9 A. M. her temperature was 102° F., pulse 116, respirations 26. There was marked clinical improvement after the transfusion and the child was discharged three days later in good condition.

Case 2 — (From the service of Dr. Garfield Duncan, Pennsylvania Hospital, Philadelphia, Pa.) E. W., a diabetic colored woman, age 25, was in a deep coma when first observed by us. The blood sugar was 530 mg. per 100 cc. of blood. Attempts had been made to give insulin and fluids intravenously but, since the veins were collapsed, it was not possible to do it. The patient had been given several injections of insulin intramuscularly, apparently without effect. At 9 A. M. of December 30, 1940, a needle was inserted in the manubrium of the sternum and a small amount of blood-marrow mixture removed. At 9:02 A. M. 120 units of crystalline zinc insulin were injected followed by an infusion of 1,000 cc. of 5 per cent glucose at the rate of 11 cc. per minute. At 9:16 the pulse was felt at the wrist and five minutes later it was 96 per minute, regular and of fair volume. The patient came out of the stupor and answered questions. The infusion of 5 per cent glucose was continued at the regulated rate of 8 cc. per minute until the patient had received 1,500 cc. in about three hours. By 11 A. M. her circulation again began to fail but through a misunderstanding the insulin was given intramuscularly instead of through the sternal needle. She died at 12:15 P. M.*

Case 3 — (From the service of Dr. Frank R. Lock, Bowman Gray School of Medicine, Baptist Hospital, Winston-Salem, N. C.) M. H., age 45, female, white. On September 3, 1941, at 8:30 A. M. this patient underwent a perineorrhaphy and abdominal hysterectomy, under pontocaine spinal anesthesia. The operation proceeded without any complications. The patient's blood pressure was well maintained throughout, and she returned

* This case was previously reported in greater detail in *Surg., Gynec., and Obst.*, 73, 281, September, 1941.

to her room in good condition. Between 9 45 A M and 1 P M her blood pressure declined gradually until at 1 15 a reading could not be obtained. There was no evidence of hemorrhage anywhere. At 1 30 P M it was possible to start an intravenous infusion of 10 per cent glucose (1,000 cc) and 250 cc of plasma. The impression was that the patient's peripheral circulatory collapse was probably due to pontocaine. The blood pressure remained low until the end of the infusion at 3 30 P M. At 4 P M it was not possible to re-enter the veins and an infusion of 500 cc of blood and 500 cc of 5 per cent glucose was started through the manubrium of the sternum. While the infusion was flowing in by gravity the blood pressure dropped to zero. At this point the infusion apparatus was removed and the blood and glucose were injected through the sternum with a syringe. Between 5 and 5 20 P M 400 cc of blood, 250 cc of plasma and 500 cc of 5 per cent glucose were injected through the sternum (total amount 1,150 cc in 20 minutes, or 57.5 cc per minute). Administration of the fluid was continued by slow drip afterwards. Two doses of digifoline (five cat units) were then injected through the sternal needle. By 8 20 P M there were still signs of circulatory collapse, the abdomen was tense, the patient quiet and there was on palpation definite evidence of intra-abdominal hemorrhage. At 8 30 P M the patient was taken to the operating room and the abdomen was reopened under light ether anesthesia. There was a large amount of blood in the abdomen, coming apparently from the right broad ligament. While the vessel was being located and tied the circulation was maintained by injecting 500 cc of blood through the sternal needle. At the end of the operation the blood pressure was 140/80, it was then possible to give 1,000 cc of blood intravenously (Fig 3).

Case 4—(Reported by courtesy of Dr Albert Davis, Camden, N J) M McG, female, white, age 32, had a large pelvic abscess which ruptured while she was being moved to the hospital on October 30, 1941. At 2 P M of that day a celiotomy was performed, there was extensive lower abdominal peritonitis. Cigarette drains were inserted and 8 Gm of sulfanilamide were left in the abdominal cavity. Immediately after the operation a transfusion of 500 cc of blood intravenously and 1,000 cc of salt solution by hypodermoclysis were given. Her condition was fair then, but by late afternoon of the next day the patient was in profound circulatory collapse, the pulse was 148, scarcely felt at the wrist, the skin was clammy, the lips cyanotic. Attempts to give her fluids by vein were unsuccessful for several hours, finally a needle was inserted into the vein but after 75 cc of blood was given no more would run in. A marrow infusion needle was then inserted into the sternal manubrium and 425 cc of blood was administered by gravity over a period of 75 minutes. This was followed by 250 cc of 10 per cent glucose solution and 1,000 cc of 5 per cent glucose, or a total of 1,675 cc over a period of 13 and one-half hours. At the conclusion of the intramedullary infusion the patient was visibly improved and it was then possible to administer all subsequent fluids intravenously. For the following five days the patient's condition was critical but there were no more episodes of acute circulatory collapse and it was possible to give all further intravenous therapy without difficulty.

COMMENT—Much of the medication given at present to patients with acute failure of the peripheral circulation is ineffective because it is administered by intramuscular or subcutaneous injection. Fluids, rapidly administered intravenously, are often the only means of restoring the circulation to normal. Though these principles are generally recognized, execution of the indicated measures is often made difficult or impossible by the very disorder of the circulation which requires treatment. Under these circumstances, the delay involved in locating a vein and in the attempts to introduce a needle into it, may jeopardize any chances for recovery from the acute circulatory collapse. When all required equipment is available and ready, it should be possi-

ble to start an intramedullary infusion or injection within less than three minutes after penetration of the skin by the needle. In contrast with venesection no incision of the skin or any special after-care of the wound is necessary, no veins are ligated, thereby depriving the patient of their use at some future time.

The method may be useful in the emergency treatment of mutilated patients or in those whose skin has been burned so widely as to make it impossible

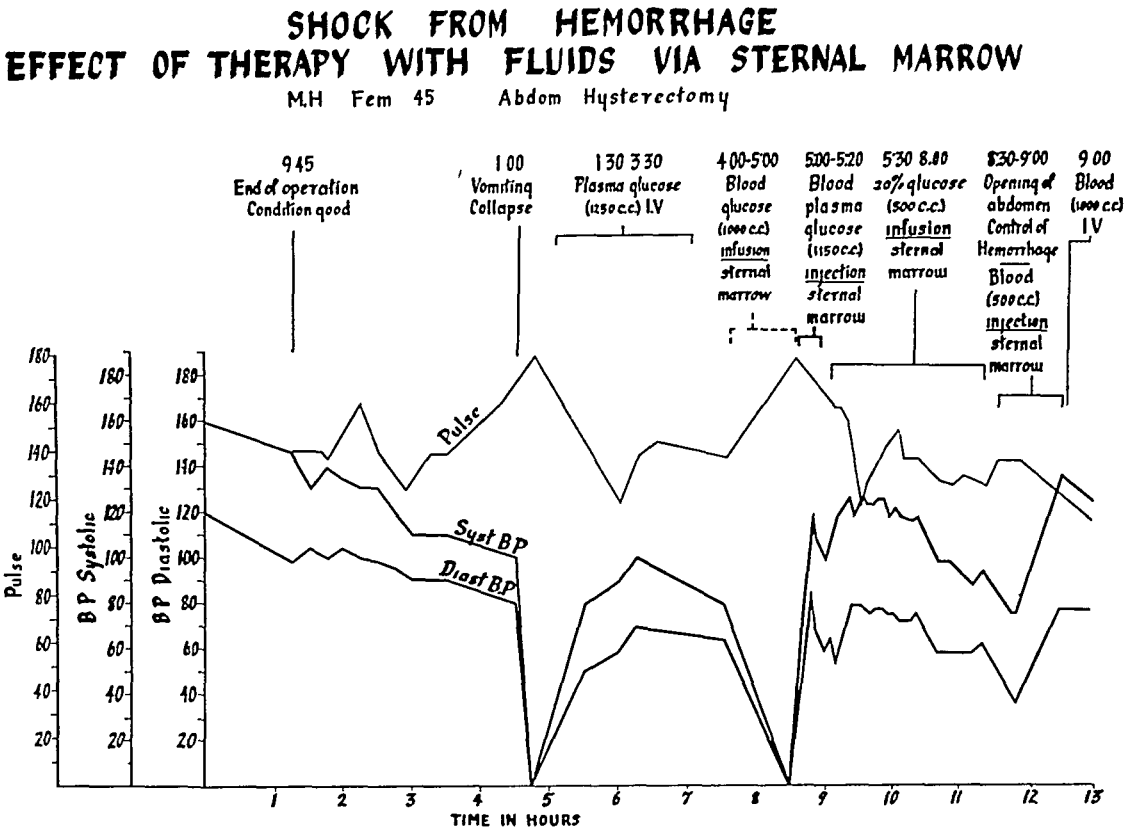


FIG. 3—Changes in the pulse and blood pressure of M. H. (Case 3)

to use the veins of the extremities. Since the needle, once in place, remains fixed, it allows continuation of an infusion while the patient is being transported from one place to another, without fear of displacing the needle.

Even though one is working under pressure of the existing situation, the precautions enumerated in detail elsewhere^{2, 3} should be strictly observed. No fluid should be injected unless marrow is clearly obtained by aspiration. Sturdy needles, preferably especially made for the purpose, should be used to minimize the danger of bending or breaking. Familiarity with the anatomic landmarks should be obtained by practice on a fresh cadaver.

SUMMARY

In four patients with acute failure of the peripheral circulation, the injection of blood, fluids or drugs via the bone marrow was followed by a prompt recovery from the state of collapse. The intramedullary route is indicated

whenever veins are not available and a rapid introduction of fluids into the central circulation is urgently needed

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BRIEF COMMUNICATIONS AND CASE REPORTS

ARTERIAL EMBOLECTOMY

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THE SUCCESSFUL REMOVAL of an arterial embolus is sufficiently unusual to warrant its report

The most common source of embolization of the arteries is conceded to be the left side of the heart^{1, 2, 3} About 50 per cent of the cases are associated with mitral disease³ The localization of the embolus is most frequently in the common femoral artery The case related below illustrates the value of heparin and passive vascular exercises (pavæx treatment) when combined with embolectomy

Case Report—Hosp No 40-1875 A E, white, female, age 31, was admitted to the Medical Service of the hospital, June 17, 1940, complaining of abdominal pain, nausea, and vomiting of three days' duration She was a known cardiac for four years, but had been without treatment for seven months prior to her admission Physical examination revealed the heart enlarged to the left, with a presystolic and diastolic thrill at the apex The patient was fibrillating at a rapid rate There were numerous moist rales at both lung bases The liver was moderately enlarged and tender There was no peripheral edema The diagnosis at this time was rheumatic heart disease, with mitral stenosis and insufficiency, and auricular fibrillation The patient's heart rate did not slow with digitalis She was then placed on quinidine and the rate dropped markedly

On June 25, 1940, the patient complained of coldness and pain in both calves and numbness of her entire left lower extremity Physical examination at this time revealed absent pulsation of the dorsalis pedis artery Two days later, the pain in her left calf and foot became more severe The dorsalis pedis artery presented no pulsation and the pulsation of the popliteal was hardly perceptible Her left leg from the knee down was numb and sensation was absent The leg became cyanotic and cold There was a faint pulsation at the femoral artery just below Poupart's ligament In view of this evidence, the patient was transferred to the Surgical Service that night, and an arterial embolectomy was performed by one of us (F W B)

Operation—Under local anesthesia, an incision was made along the inner aspect of the left thigh in the upper one-third of the course of the femoral artery The femoral artery was visualized and was found to be in spasm and not pulsating Stay-tags were put around it to control bleeding and the vessel was opened It did not bleed on opening A fine suction tube was inserted and suction applied There was no blood or clots removed from the proximal portion of the artery Some dark venous blood was obtained from the distal portion of the vessel The incision was then extended upward and the femoral artery was inspected at a level, one inch below Poupart's ligament There, the artery was found to be much more dilated and its walls were distended by thrombi An incision was then made over this portion of the femoral artery An organized thrombus was removed by forceps, however, active bleeding did not occur, so a glass tube was inserted to about the level of the bifurcation of the aorta and aspiration brought pieces of soft clot followed by active arterial bleeding Immediately thereafter, pulsation started and continued down to the site where the artery was first incised The wound was then

irrigated with heparin and the incisions of the vessel were closed by interrupted fine vaselined silk sutures. The skin incision was closed with Stewart stitches.

Postoperative Course—Upon returning from the operating room at 1:30 A.M., June 28, 1940, the patient was given 30,000 units of heparin. This was repeated at 4 P.M. and 8:30 P.M. The next four days the patient was given 30,000 units of heparin per day. The heparin was given with normal saline, which was being administered by continuous intravenous drip at the rate of 3,000 cc. per day. On the day following the operation, the leg appeared a little warmer. The patient, however, complained of a great deal of pain. The entire limb was then inserted into a pavaex machine, after which the patient appeared to be more comfortable. The limb was kept in the machine for varying periods of time, from two to four hours, three times a day. The machine was set at two cycles per minute, with a positive pressure of 20 and a negative pressure of 60, so that the ratio of negative to positive pressure was 3:1.

On June 30, 1940, the foot appeared warmer than prior to operation, although still cooler than the other one. It was not quite as pale. The area of anesthesia extended to about five inches below the knee. There were no palpable vessels in the entire limb except the femoral artery. Examination three days later revealed sensation returning, and the foot was slightly warmer. However, it was still discolored, particularly over the heel. A sloughing area appeared above the anterior aspect of the knee where the rubber cuff of the pavaex machine had been applied. However, from this time on the patient progressively improved so that she was discharged, August 15, 1940, in good condition.

It is not our purpose to completely review embolectomy of the vessels of the extremities. This subject has been well reviewed elsewhere^{1, 3}

The occurrence of an embolus induces a certain degree of spasm in the vessel wall involved. The drop in pressure distal to the point of occlusion further diminishes the caliber of the lumen. This, associated with the retarded blood flow, endangers the efficiency of the collateral circulation. When the embolus becomes adherent, it injures the intima, this favors coagulation of the blood. If this process continues, the extending clot may obstruct the collateral vessels.

The use of heparin as a physiologic anticoagulant is well outlined by Mason.⁴ Best⁵ has demonstrated how it prevents thrombosis. After embolectomy has been accomplished, failure to acquire a cure may be the direct result of secondary thrombosis. Murray⁶ has demonstrated that heparin is nontoxic in humans, that it is useful in diseases complicated by intravascular clotting, and that it will prevent thrombosis and clotting in blood vessels.

Since its properties have been demonstrated, many successes have been reported following its use. Murray⁷ reports 440 patients treated in the hospital with heparin in whom thrombosis and embolism did not occur. He also reports 12 successful embolectomies in which heparin was used. He suggests administering heparin at the time of operation and for three to four days following.

Herimann and Reid^{8, 9} have demonstrated the benefits derived from the pavaex treatment. This procedure can be carried out without discomfort or untoward effects.

We agree with Lund¹⁰ that the best results are obtained when early

embolectomies are performed Heanley¹¹ concurs in this opinion, but again emphasizes the advantages offered by heparin

Burnett¹² performed a retrograde extraction of an embolus, however, without success

SUMMARY

This case illustrates the successful removal of an embolus from the femoral artery, 48 hours after the onset of symptoms, by a retrograde suction procedure The success is further attributed to the combined use of heparin and pavaex treatment

We wish to thank Roche-Organon for supplying us with "Liquaemin" (heparin)

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AN APPARATUS FOR CLOSED DRAINAGE OF THE VENTRICULAR SYSTEM

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CHRONIC increased intracranial pressure has usually been combated by repeated tapping of the ventricular system or by continuous drainage into sterile gauze *via* a cannula or catheter left *in situ*. Both means of drainage, no matter what precautions are taken, submit the patient to a risk of sepsis. In order to avoid this hazard, a continuous closed system of drainage was devised. It is in no sense an original idea but merely an improvement upon various devices that have been employed in many clinics.

This apparatus has been successfully employed as a temporary means of decompression where block has existed caudad to the foramen of Monro. Its use is indicated when dehydration and inanition must first be dealt with by supportive measures before operation can be undertaken. It is further indicated when diffuse pressure clouds localization and ventriculography might prove to be too drastic as a first step in an investigation. The difficulties arising from edema in a partially removed malignancy and consequent block of the ventricular system occurring during a course of roentgenotherapy may often be surmounted by this type of drainage. It has further been of aid in judging the adequacy of skin for closure when removal of a large meningocele is contemplated in a case of arrested hydrocephalus. The meningocele may be gently collapsed, allowing an accurate estimation by manipulation of the surrounding skin. When excision of such a type of meningocele has been carried out and closure effected under any degree of tension or by undercutting, it has proved to be of value in preventing spinal fluid leakage from or extravasation beneath the wound.

Description of Apparatus *—The apparatus consists of a flanged, sterling silver cannula (A) which is blunt at the end, equipped with a stylet and threaded adaptor. Cannulae have been made up in the following lengths 4, 5, and 7.5 cm. Light, transparent rubber tubing connects the adaptor with a "three-way" stop-cock (B) and in turn with a 250 cc burette. The burette is closed with a tightly packed plug of gauze. Autoclaving is the preferable means of sterilization.

Operative Procedure—Bilateral posterior parietal bur-holes are made under novocain anesthesia, with or without the support of avertin, depending upon the circumstances. After the dura and arachnoid are opened, a brain needle is used to determine the depth of the ventricle. With this knowledge, a cannula of suitable length may be chosen. The wounds are then closed in layers, using black silk throughout. The cannula with stylet in place is next

* The cannulae were made by George C. Gebelein, 73 Chestnut Street, Boston, Mass.

placed through the closed wound. As soon as the stylet is withdrawn, the adaptor is threaded into the cannula. A square of gauze, which has been slit to its midpoint, is placed between the flange of the cannula and the wound. Several similar squares are placed above the flange. Fluffs are then wound loosely about the lower 3 cm. of tubing in such a manner as to guard against contamination but yet avoid kinking or compression. The dressing is secured beneath a turban of woven bandage. This is, in turn, stabilized by a chin-strap of flannel secured at intervals with safety pins as far as the midline. The tubing is then looped beneath a small safety pin in order to avoid direct traction on the cannula. When the patient is placed in bed he should lie on the side opposite the cannula. The burette is hung on an adjustable arm at the head of the bed.

Should previously made bur-holes exist, novocain may be infiltrated and a small stab wound made down to the dura. The dura should be pierced by a No. 18 lumbar puncture needle, and enlarged by the passage of a brain needle, used in ascertaining the depth of the ventricle. The appropriate cannula may then be passed down this tract without trauma. The next steps have already been described. It is also possible to pass the cannula through widely separated sutures in order to establish drainage, if previously made bur-holes do not exist, or if the making of bur-holes is contraindicated.

Maintenance of Drainage—The patients are afforded great subjective relief by this means of decompression. Judgment concerning restraint of the patient's aims must be made, depending upon the age and mentality of the individual. It is wise to bolster up all types and ages of patients on the side opposite the cannula to avoid compression or tension on the tubing. Doughnut-shaped rings of gauze and cotton are of use in stabilizing the head and protecting the dependent ear.

Cultures and cell counts are made bidaily. Fluid is withdrawn as often as the 100 cc. mark in the burette is reached, in order to prevent any possible contamination of the upper portion of the burette.

The toilet of the stop-cock is worth mentioning. Except when in actual use, a sterile gauze covering should be over it. Before withdrawing fluid for cell count and culture, the stop-cock is prepared with ether (3.5 per cent), iodine, and 70 per cent alcohol, applied in that order by means of saturated sterile swabs. Cell counts are taken after the first 5 cc. of fluid have been withdrawn. Cultures are taken after 25 to 30 cc. have been withdrawn, in order to prevent inhibition of any possible growth by antiseptic solutions used in the preparation of the stop-cock.

Seventy-two hours of drainage through one bur-hole is the maximum time advisable. Sepsis has not occurred within this time limit in our experience. A fresh apparatus may then be set up, using the other bur-hole if further drainage is necessary.

Approximately normal intracranial pressure may be maintained by adjusting the burette holder at the head of the bed at frequent intervals, in order to maintain the *in vivo* level of fluid at the level of the uppermost lateral

ventricle In this manner, the patient is spared the sudden upsetting changes of pressure that occur when intermittent tapping is carried out

In the hands of an alert house staff and competent nursing staff, this apparatus has been very easy to handle Children seem to realize the benefit it affords them and seldom have revolted against it Observation by nurses

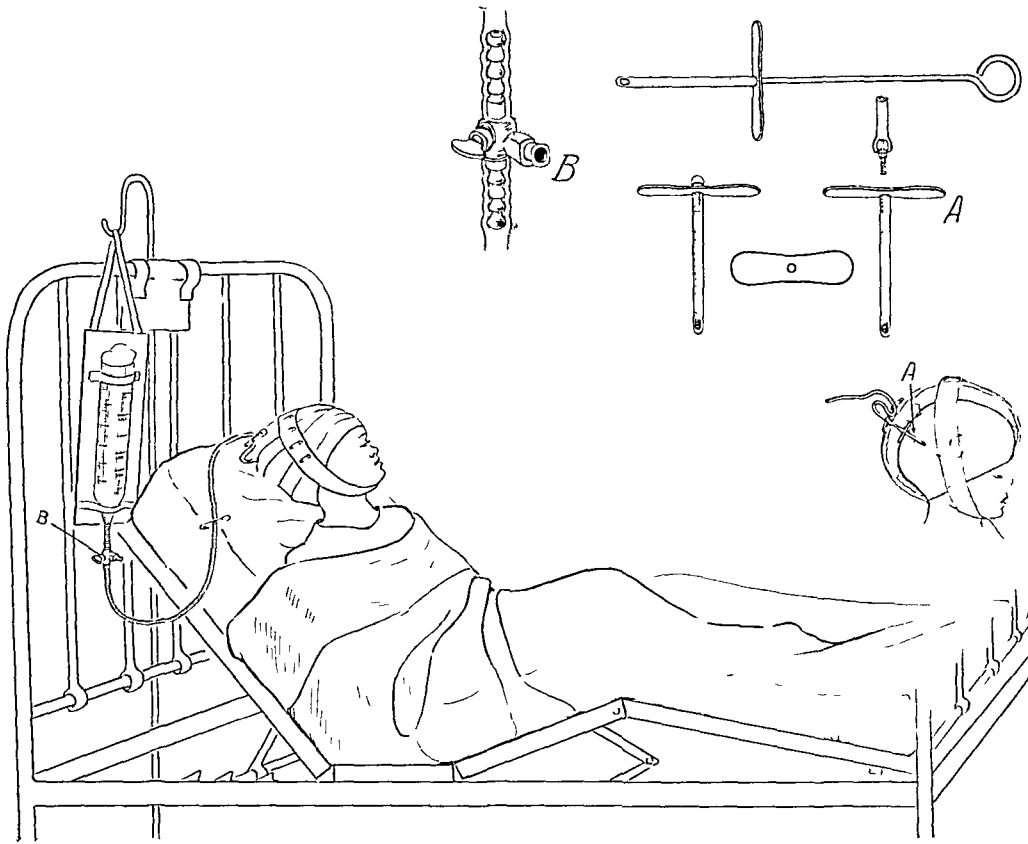


PLATE I—Position of patient in bed with apparatus set up Note burette plugged with gauze hanging from an adjustable arm A Silver cannula with threaded adaptor and stylet A¹ Position of cannula in ventricular system and overlying dressing B 'Three way' stop cock B¹ Position of 'three way' stop cock in system

at ten- to 15-minute intervals has proved to be sufficient to ward off any inequality of pressure or slipping of the well-bolstered patient from position which might jeopardize the continuity of drainage

We have described this system of ventricular drainage thinking that it might be of aid to others

AMPUTATION FOR OSTEOGENIC SARCOMA OF LOWER END OF FEMUR

NINE-YEAR FOLLOW-UP OF TWO CASES

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Case 1—Hosp No 83115 H S, age 16, was admitted to St Luke's Hospital, November 24, 1930, with a history of swelling of the right knee of three months' duration steadily increasing. This became painful one month before admission and during this period the pain increased. Limitation of extension of the right knee developed and walking became more and more difficult. There was no preceding history of trauma. He had always enjoyed good health.

Examination showed a fusiform swelling from the knee to a point about 12 cm up the femur. This was hard and seemed to involve the bone only and not the overlying soft tissues. No inguinal nodes were palpable. There was 30° limitation of extension of the knee joint.

Operation was performed one week after admission, under nitrous oxide anesthesia. A biopsy of the bone growth was taken and a frozen section was reported as osteogenic sarcoma. A high thigh amputation was then undertaken, and the flaps closed without drainage.

The postoperative course was exceedingly smooth and remarkably painless. The stump healed *per primam* and he was discharged on the twelfth postoperative day. He had no preoperative or postoperative radiotherapy.

Pathologic Examination—Path No 40815 Dr Leila C Knox. The growth is largely of the spindle cell type but in many areas it shows the differentiation characteristic of periosteum. The nuclei are not extremely numerous, are elongated or triangular in outline, and there is considerable myxomatous material between the cells. There is also a moderate amount of collagen in very finely divided bundles. Between these are occasionally very large nuclei, indicating a far more malignant type of growth than some of the fibrous areas would suggest. In these large cells mitotic figures are occasionally to be seen (Fig 1).

The lining of the large cavity in the bone consists of tissue of the same type as that forming the main tumor mass. Fragments of necrotic bone are included in this. The sections do not show any osteoid tissue, but the close resemblance to periosteum indicates its osteogenic derivation. (This case has not yet been registered with the Bone Sarcoma Registry.)

Case 2—Hosp No 83108 S G, male, age 22, was admitted to St Luke's Hospital, November 21, 1930, complaining of pain in the inner lower right thigh, first noticed about eight months before admission. Two months later he found a "slight swelling of the bone" in this area. At first the swelling increased slowly, but for the last three months it had seemed to grow much more rapidly. There was no history of trauma preceding the appearance of the lesion. During the two weeks before admission, he was given three roentgen ray treatments over the site of the lesion, at Memorial Hospital. His previous history was negative except for the fact that he had had rheumatic fever at the age of 16.

Examination showed, on the medial aspect of the right thigh, just above the medial epicondyle, a bony tumor which was not tender and seemed definitely fixed to the underlying bone. The overlying skin appeared normal and moved freely over the growth. The growth was estimated to be about 3.7 cm in size. Preoperative roentgenograms were not taken at St Luke's as they had been made elsewhere. On the day after admission

a biopsy was taken of the growth. This was reported as an osteogenic sarcoma of the femur. Two days later, under nitrous oxide anesthesia, a high, right thigh amputation was performed, and the flaps were closed without drainage.

Except for a postoperative temperature of 104° F on the first day after operation, which gradually dropped to normal in a week, his convalescence was smooth. The wound healed *per primam* except for moderate drainage of serum, and the patient left the hospital three weeks after the operation.

Pathologic Examination—Path No 40796 Dr Leila C Knox. The growth is derived from the periosteum and is characterized by the formation of large quantities of

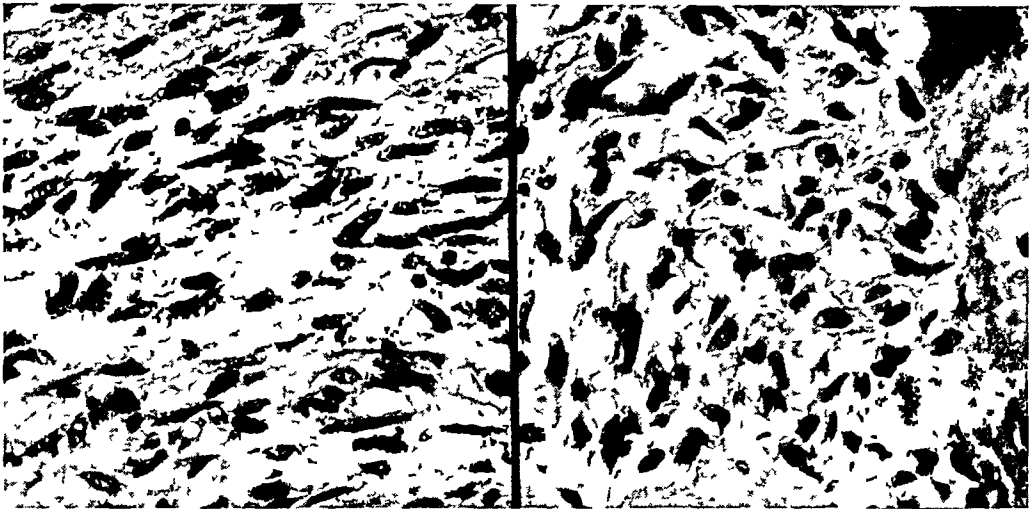


FIG 1

FIG 2

FIG 1—Case 1. Photomicrograph showing the predominant type of growth. Large periosteal fibroblasts are arranged in a slightly laminated manner but differ from each other in size and shape and all of them are larger and more irregular than normal cells. Structures resembling bone cells are seen occasionally. Osteoid tissue is not included in this section. (X750)

FIG 2—Case 2. Photomicrograph showing the tumor to be composed of large connective tissue cells, very irregular in size, shape and arrangement, many of them surrounding newly formed osteoid areas. An occasional bone cell is included. (X750)

bone in a moderately cellular connective tissue matrix. Some of these areas are extremely vascular, containing large blood sinuses, and around these bone is forming in small quantities. In some places the walls of these sinuses are not lined with endothelium, but only with a connective tissue type of tumor cell. There is only a little old pigment, but some of the sections show numerous endothelial giant cells. There are also osteoclasts which may be distinguished from the phagocytic cells. In some areas the connective tissue is myxomatous and differs little from the normal. In others, it is distinctly cellular while in still others the nuclei are irregular, large and aplastic. The growth is composed of about equal parts of osteoid tissue and of spindle cell connective tissue, and is unquestionably malignant (Fig 2). (This diagnosis has been confirmed by Dr Francis Carter Wood, but has not yet been registered with the Bone Sarcoma Registry.)

He was readmitted January 24, 1936, four years ago, because of a lump in the stump, first noted by him ten days previously. Otherwise he had been entirely well. Roentgenograms of the chest were made and proved to be negative.

On the day after admission, under nitrous oxide anesthesia, an incision was made over the mass which he had discovered in the stump. This proved to be muscle which had apparently separated and retracted from its point of union with the other muscles in the stump. A biopsy of the muscle mass was made and reported "regenerative changes in muscle, no tumor in sections."

DISCUSSION —DR FRANCIS CARTER WOOD (New York) Doctor Wood said that, with reference to Doctor Solley's cases, one could use the old law term, "the thing speaks for itself." The extensive bone destruction and the morphology of the tumors is perfectly definite. On the other hand, Doctor Wood made the point that although the diagnosis was made in his own laboratory, a bad habit has grown up of making a diagnosis on most bone tumors and calling them "osteogenic sarcoma." In Doctor Solley's first case there was a periosteal spindle cell sarcoma, and it would have been better to have so named it rather than to have concealed the morphology under the general term "osteogenic sarcoma." The second tumor was rightly called osteogenic sarcoma, and interested Doctor Wood very much because of the fact that the surgeon of to-day is assuming a position of hopelessness in the treatment of these bone sarcomata. There is nothing to be accomplished by radiating them, inasmuch as osteogenic sarcoma, with cartilage production, is not susceptible to radiation. It is true that the salvage, even with prompt surgery, is small, but if one continues to attempt to salvage these with roentgenotherapy all will die. These two patients were snatched from inevitable death by fairly prompt and extensive surgery and constitute excellent illustrations of the situation.

GLOMUS TUMORS

REPORT OF FOUR CASES IN SAME FAMILY

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GLOMUS TUMORS have been recognized as a clinical entity since about 1912, when Wood, of Edinburgh, described several cases of "painful subcutaneous nodules" of the extremities. In 1924 Masson¹ published the first definite description of the pathologic and clinical characteristics of glomus tumors. He defined and described the histology and physiology of the normal glomus with a demonstration of the curious neurovascular muscular structure, and so established glomus tumors as definite entities. Since his classic paper, the lesion has been thoroughly investigated. An excellent and exhaustive description of the condition, with a review of the literature was published by Oughterson and Tennant² in 1939.

While it is known that glomus tumors may occur anywhere in the body, a study of the literature reveals only one case of the lesion in the thigh. The vast majority are to be found in the upper extremity—the hand, nails or the fingers. The glomus tumor has characteristic clinical signs. It is usually a small, superficial pigmented nodule exquisitely tender and painful. The nodule varies from a few millimeters to a few centimeters in size, always superficial, and since it is made up of blood vessels, pigmentation varies according to its depth from a deep purple to varying shades of red, which may even be almost absent in the common subungual type. The tumors are generally found on the extremities, commonly the upper and rarely on the face and trunk. Since the time of Masson, the subungual form has been the classic type but these tumors are now recognized in many other regions, two cases having recently been reported by Grauer and Burt⁴ on the penis. The most characteristic sign is the peculiar severity of pain and tenderness, paroxysmal, agonizing throbbing and associated with modalities of unusual intensity by changes in position, heat or cold, *etc*, and extreme sensibility to contact and pressure. These typical findings, varying in degree, should serve to establish at least a presumption of glomus tumor in the diagnosis of superficial vascular tumors (fibroma, angioma, varix and malignant tumors).

Clinicians have noted in the past that the lesions were often accompanied by the phenomenon of increased warmth throughout the affected area. This was not fully investigated however until 1937, when an excellent study was reported by Stabins, Thornton and Scott³. They showed that the increased

temperature was apparent in the entire limb and not restricted to the area of the tumor. Their suggestion was that the mechanism was one of vasodilatation of the peripheral vessels due to a reflex, the efferent arc of which is not limited to the peripheral nerve field in which the sensory stimuli arise. Thus it would seem that the vasodilatation is excited by sensory stimulation which acts on the trigger mechanism. This is unusual, in that the common effect of painful stimulation is one of vasoconstriction. It may be that the

FIG 1

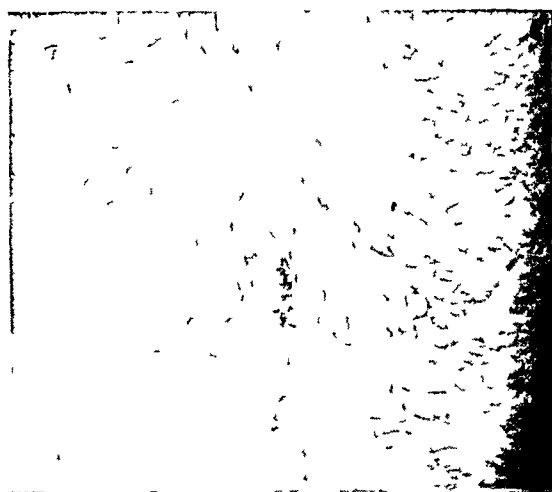


FIG 2



FIG 3

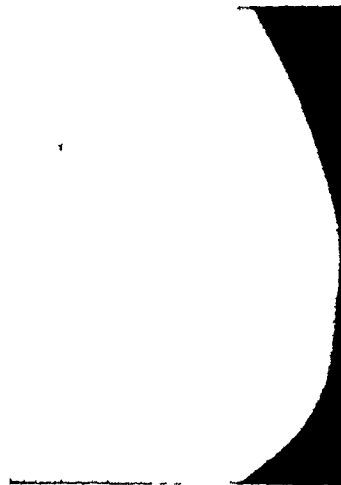


FIG 4

FIG 1—Case Mr. D. Showing scar on thigh following removal of tumor.
FIGS 2 and 3—Case Mr. D. Photomicrographs of lesion removed ($\times 400$ and $\times 100$, respectively).
FIG 4—Case Mrs. J., age 31. Showing lesions on left upper arm.

nerve elements of the glomus are parasympathetic in nature or perhaps pre-ganglionic sympathetic fibers. The surgeon should consider glomus tumor when dealing with a highly vascular, rather small tumor on the surface which presents severe pain and tenderness peculiarly out of proportion to the size, distinction and appearance of the lesion. All such tumors should be considered as possible glomus tumors and the final diagnosis made by the laboratory. It is quite probable that the tumor is not as rare as the literature would indicate. Many excellent clinicians are not familiar with the lesion.

and many such tumors are no doubt overlooked or treated as varicosities, angiomas, etc

Nothing has been suggested as to any familial tendency in this condition. In our study we are presenting four cases occurring in a single family. The distribution was as follows: (a) Paternal aunt—lesion on wrist; (b) Sister—four on upper extremity; (c) Brother—one on thigh; (d) Daughter of sister—one on lower leg.

Only one case came to operation—that of the brother, a medical student, age 22. He stated that the small discolored area in his thigh was noted when he was an infant. However, during the past eight years it had become more elevated and painful, the pain being sharp and of a cutting nature, especially when the lesion was touched. Examination showed a small bluish nodule, 2 cm in diameter, on the anterior surface of his left thigh. This was removed surgically (Fig. 1) and the accompanying photomicrographs reveal the morphology of the tumor (Figs. 2 and 3). The other members of the family showed similar lesions with the same symptom complex. The sister (Mrs. J.), age 31, has three lesions in the region of the left upper forearm and lower arm, and one on the dorsum of the proximal phalanx of middle finger (Figs. 4, 5 and 6). The temperature readings on Mrs. J. were as follows:

Room temperature 71.5° F			
(a) Before immersion in cold water			
Fingers	(right) 79.5° F	(left) 87.4° F	
Palm	83.0° F	88.0° F	
Wrist	83.8° F	88.6° F	
(b) Five minutes following immersion			
Fingers	(right) 74.6° F	(left) 80.0° F	
Palm	79.2° F	84.0° F	
Wrist	80.0° F	84.0° F	
Readings on Ann. J. were as follows:			
Room temperature 67.5° F			
Right foot	76° F		
Left foot	72° F		

After irritation of the lesion the temperature of the right foot rose to 79° F.

SUMMARY

We have presented cases of glomus tumors appearing in four members of the same family. The sites of occurrence are rather varied. Temperature readings are presented in two instances, to illustrate the likelihood that the lesion produces temperature changes and that the glomus body exerts an influence in regulating surface body temperature. We feel that the lesion may not be as uncommon as supposed but that unfamiliarity with the condition by clinicians may have caused many tumors to be overlooked and incorrectly diagnosed. Facilities are usually available to most surgeons for recording surface temperatures, and in these tumors surface temperature readings offer diagnostic aid. This test determines that pain, which is a prominent symptom of the lesion, is associated with vasodilatation; we are reporting the occurrence of glomus tumors in four members of the same

family presenting widespread distribution of the tumors, all of which present, however, rather uniform and typical characteristics

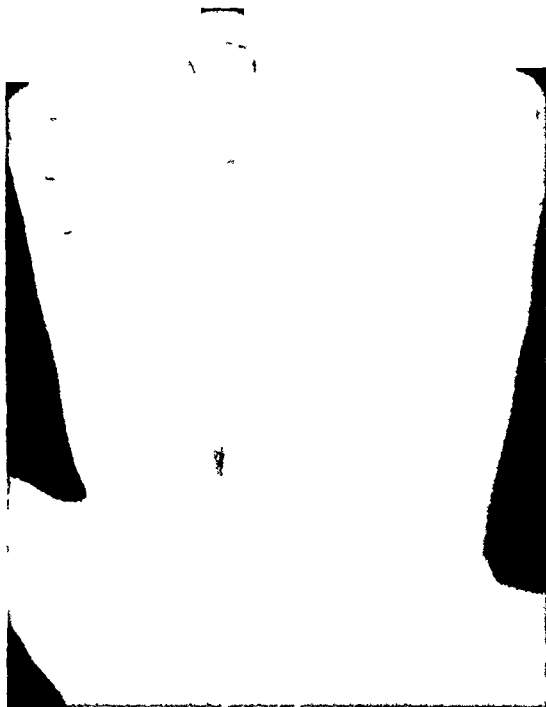


FIG 5

FIG 5—Case Mrs J, age 31 Showing lesion on dorsum of proximal phalanx of right middle finger



FIG 6

FIG 6—Case Ann J, age five Showing lesion on lower right leg

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CENTRAL CHONDROSARCOMA OF THE FEMUR^{*}

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CENTRAL CHONDROMATA, or chondromyxomata, are common lesions in the small bones of the hands and feet, the ribs, and spine. They are benign and usually single lesions. According to Geschickter and Copeland¹ "True central chondromata of the long bones are extremely rare, and it is doubtful whether such a diagnosis is justified on the basis of the roentgenogram alone. In nearly 2,000 tumors of the bone there are but five well-established cases, and in these the resemblance is so close to malignancy in the roentgenogram, and the tendency for the lesion to recur and to be cured only by radical operation is so great, that there is little practical harm in classifying these tumors as forms of chondrosarcoma."

For treatment, they recommend curettement followed by adequate cauterization, either thermal, or chemical with 50 per cent zinc chloride. Recurrences in the case of large bones have followed this treatment in about 25 per cent. They advise postoperative radium therapy.

Case Report—J. M., female, white, age six, was admitted to the Stuyvesant Square Hospital (now the Skin and Cancer Unit of the New York Post-Graduate Hospital) in December, 1933. She was said to have commenced to walk at 14 months and to have walked normally until about four years of age. Since that time, two to three years, she had had a left lower extremity limp which the child said was because it hurt her. For about one year before admission the parents had carried the child most of the time on account of the pain and limp. There was nothing relevant in family or past history.

Examination showed no abnormalities except the left upper thigh, which was considerably larger than the right, while the remainder of the extremity was smaller. On palpation the enlargement seemed to be bony, was smooth, not tender and with no inflammatory signs.

Roentgenologic examination showed a central lesion, involving the greater and lesser trochanters and extending three inches down the shaft of the femur. There was general expansion of the bone over this area with no break in the cortex except at one point where there was a suggestion of an incomplete fracture. The involved bone has translucent areas marked out by lines and particles of calcification which give it a multiloculated appearance. There is no evidence of periosteal involvement (Fig. 1). The whole skeleton was examined roentgenologically and no other lesion found. Wassermann and Kline tests were negative. Complete blood count, urine findings, and temperature were normal.

The diagnoses considered were Ewing's tumor, giant cell tumor, bone cyst, and osteitis fibrosa cystica. The case did not seem to conform to any of these.

Operation—January 5, 1934. An incision was made over the great trochanter. Nothing abnormal was encountered in the soft parts. Through a small opening in the cortex, which was not over one-sixteenth of an inch thick, tissue was removed for frozen section. Grossly and microscopically, this seemed to be cartilage. A larger window was then made on the outer aspect of the great trochanter and bluish-gray, firm material was curetted out readily until apparently firm bone was felt on all sides. A cavity about $4\frac{1}{2} \times 1\frac{1}{2}$ inches was left involving greater and lesser trochanters, part of neck, and

^{*} Presented before the New York Surgical Society, December 6, 1939.

upper third of shaft No cauterization was undertaken and no bone chips were inserted The periosteum and soft parts were sutured and a plaster spica applied

Pathologic Examination—Microscopic Dr D S D Jessup Islands of cartilage with large cell spaces and a hyaline matrix, separated by small areas of fibrous tissue At one point scattered giant cells of foreign body type are found The decalcified sections show thin layers of bone forming in trabeculae along the edges of the islands of cartilage There are a few osteoclasts (Figs 2, 3, and 4) The essential growth seems to be chondroma *Pathologic Diagnosis* Osteofibrochondroma

Subsequent Course—The plaster spica was kept on for four and one-half months It was then believed that there was sufficient bone regeneration for all purposes except weight bearing A walking caliper, without hinge, was applied and was used up to one and one-half years after operation We would not have removed it at that time, on account of insufficient bone regeneration, but the child returned from the country, where she had been allowed to run about for several weeks without it, so we did not replace it We intended to give postoperative deep roentgenotherapy, but most of her first year and one-half was spent in the country and she never received but two treatments At present, she is being followed at six-month intervals with roentgenograms being taken annually When last seen, October 4, 1939, there was one inch shortening of the left femur, for which she was wearing a half-inch lift Function is complete The angle of the neck is more horizontal than on the right side, and there is outward bowing and thickening of the upper third of the left femur Bone regeneration has been slow and is far from complete The extent of the defect has seemed to correspond to growth of bone rather than to an extension of the process, although this is open to argument All three epiphyses at the upper end of the femur seem to have fused (Fig 5) The patient has no complaints and is in good health Follow-up must be continued indefinitely

The case was submitted to the Registry of Bone Sarcoma of the American College of Surgeons (BSR No 1644) It is classified as osteogenic sarcoma, chondrosarcoma type, with good prognosis Among six examiners, two classified it as benign, one diagnosed central chondroma without expression as to prognosis, and three as potentially malignant

SUMMARY AND CONCLUSION

A case of central chondroma of the femur, nearly six years after operation, is presented Although the microscopic appearance does not show char-



FIG 1—Roentgenogram showing the central chondroma of upper femur



FIG 2—S C Path No 18990 Photomicrograph of islands of cartilage showing calcification and bone formation also fibrous intervening stroma ($\times 375$)

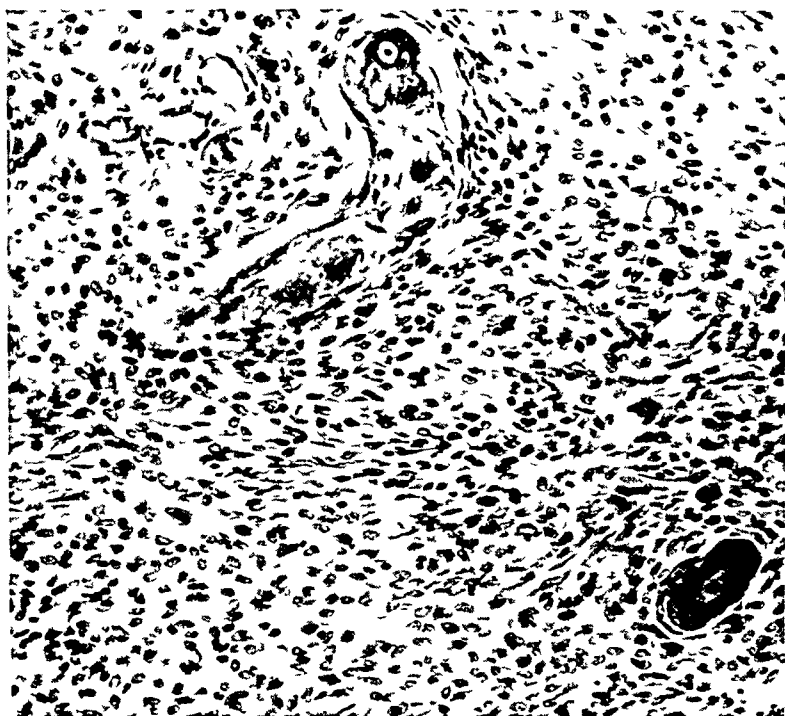


FIG 3—S C Path No 18990 Photomicrograph of an area showing a very cellular stroma but without mitoses Islands of osteoid tissue ($\times 375$)

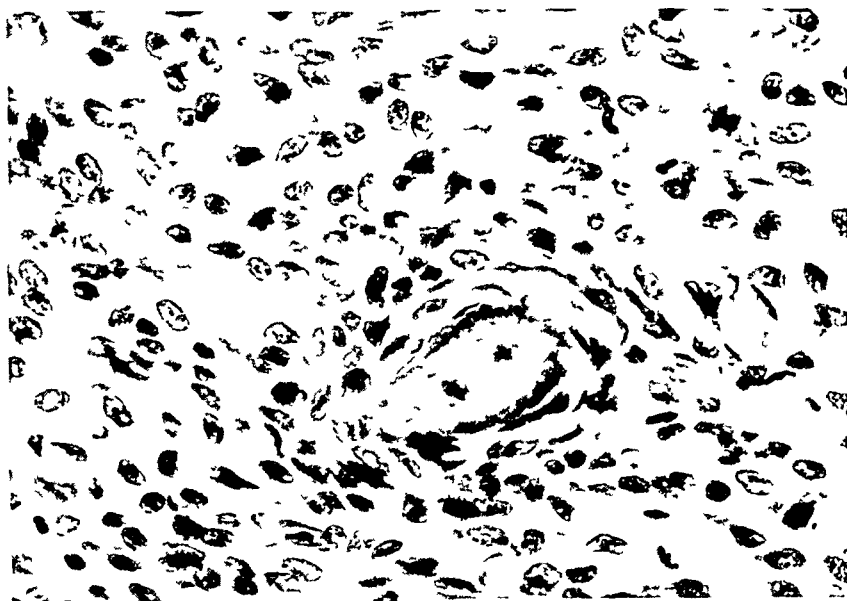


FIG 4—S C Path No 18990 Photomicrograph of a fibrous portion of the tumor showing island of necrotic bone (X875)



FIG 5—Roentgenogram showing the result five years after operation

acteristics of malignancy, experience teaches that these cases must be considered potentially malignant and should be followed clinically and by roentgenologic examination indefinitely

NOTE—Roentgenologic examination on July 8, 1941, seems to show no increased extension of the process. The patient is in excellent health at this date

REFERENCE

- ¹ Geschickter, C F, and Copeland, M M Tumors of Bone Amer Jour Cancer, 70-92, 1931

DISCUSSION—DR PHILIP D WILSON (New York) said that Doctor Kennedy's case was particularly interesting because it represented a diagnostic problem, both from the clinical and pathologic standpoint, and also because it represented an astonishingly good result from treatment of an osteogenic sarcoma by local curettement. Doctor Wilson said that, personally, he thought it wrong to use the term osteogenic sarcoma in a case like this, and that chondrosarcoma should be differentiated from osteogenic sarcoma. In retrospect, some points about the roentgenographic appearance of the tumor seem to be suggestive of chondrosarcoma. It was not characteristic of bone cyst or of giant cell tumor, and the appearance

of striae with bits of irregular calcification giving a kind of lobulated, trebeculated picture were typical of chondrosarcoma

With regard to the pathologic diagnosis, no one bone tumor is more difficult to distinguish with regard to benign and malignant characteristics than a chondroma. Doctor Wilson recalled a case that was diagnosed as a central chondroma of the humerus, yet there were three different recurrences after local operation and finally a local excision was performed followed by the insertion of a bone graft. That patient has now been well for about two years. In this case the diagnosis was a chondroma, whereas in Doctor Kennedy's case the diagnosis was chondrosarcoma and the patient has had no recurrence after local curettement—a type of treatment usually unsatisfactory with a malignant tumor. There is bound to be a good deal of disagreement as to diagnosis in a case like this. Whether the tumor is called a chondroma or a chondrosarcoma, the difference is very slight, at least from the pathologic standpoint, but in view of the subsequent course of Doctor Kennedy's case the tumor seems to have been a chondroma.

NOTICE

NATIONAL RESEARCH FELLOWSHIPS

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Fellowships for training in the field of Orthopedic Surgery, administered by the Medical Fellowship Board of the National Research Council, are open to citizens of the United States or Canada who possess an M.D. degree and who, as a rule, are not more than thirty years of age.

These fellowships open only to graduates in medicine who have completed one or more years of hospital work in clinical surgery and are planning a career in orthopedic surgery, are designed to provide opportunity for research experience in those medical sciences which will be of particular value in furthering progress in the field of orthopedics. They are not available for immediate practical training in orthopedic surgery.

The annual stipends are determined by individual circumstances and by cost of living in the location of study. The usual amount is from \$1,600 to \$2,400 per annum. The fellowships are granted for one year, but they may be renewed. Fellows are chosen at annual meetings of the Medical Fellowship Board in February, and applications to receive consideration at these meetings must be filed on or before January 1. Appointments may begin on any date determined by the Board.

Further particulars concerning these fellowships may be obtained on request. Address communications to the

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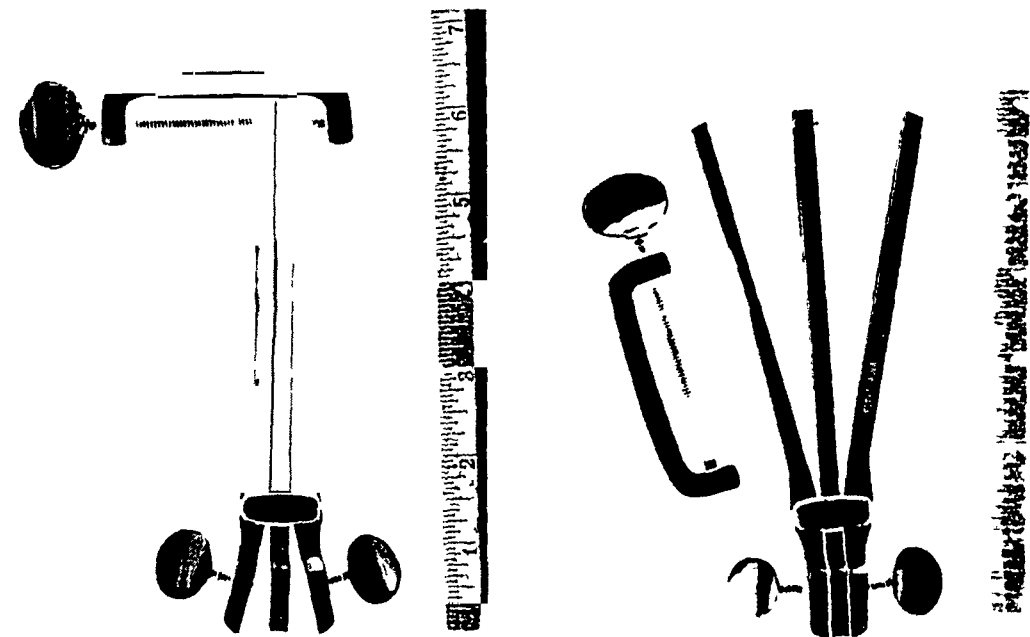
The Chairman, Division of Medical Sciences, National Research Council, Washington, D. C. *ex officio*

RANKIN-MIKULICZ OPERATION CLAMP

CARL R STEINKE, M D

AKRON, OHIO

THE RANKIN MODIFICATION of the Mikulicz-type of colon resection employs a double crushing clamp with considerable power of compression. Doctor Fred Rankin devised such an instrument but the blades do not open sufficiently wide to allow easy entrance of a heavy colon with a thick fat mesentery. Also, it has rather long handles which are sometimes inconvenient to leave on the abdomen.



FIGS 1 and 2—Photographs of clamp devised for use in the Rankin modification of the Mikulicz colon resection

The herein described and illustrated instrument made by V Mueller and Company, of Chicago, Illinois, overcomes these disadvantages. It is simple of design and not too expensive. The clamp is six inches in length, with a crushing blade four and one-half inches long and one-quarter-inch thick. For the thick-walled bowel, with a heavy or fat mesentery, a screw-clamp applied to the distal end of the blades gives strong compression power and secures the blades when this is necessary.

This instrument may also be used as a spur-clamp in the second stage of the double-barrel procedure, similar to the clamp previously reported,¹ by opening up one blade and inserting one side of the clamp into each loop of the intestine. It has a blade one inch longer than the spur-clamp formerly devised, which is a great advantage in patients with a thick abdominal wall or long bowel loop.

REFERENCE

¹ Steinke, C R Mikulicz Operation Clamp. *ANNALS OF SURGERY*, 93, 1117, May, 1931

ACUTE PERFORATION OF LYMPHOSARCOMATOUS ULCER OF THE STOMACH*

REPORT OF A CASE

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CHICAGO, ILL

FROM THE SURGICAL SERVICE OF THE COOK COUNTY HOSPITAL AND THE DEPARTMENT OF SURGERY
OF THE UNIVERSITY OF ILLINOIS, CHICAGO, ILL

INCREASINGLY frequent reports of lymphosarcoma of the stomach and the consequent gain in clarity of the clinical entity, should facilitate more successful diagnosis in the future. In spite of the rarity of the perforative lesions, three groups of these cases can be recognized in the published reports (1) Lymphosarcomatous ulcer, perforating with the clinical picture of an ordinary perforated peptic ulcer, with a suppurative peritonitis (2) Perforated lymphosarcomatous ulcer, with the clinical picture of a sealed, or *formes frustes* ulcer, with a transient acute peritonitis (3) Perforation of the tumor into the surrounding structures, with or without a sarcomatous peritonitis, but without the opening of the gastric lumen into the peritoneal cavity, to produce a suppurative peritonitis

To be sure, the literature does not always recognize the above differentiation and, as a result, the clinical concept has been somewhat confusing. Our case belongs to Group I. We have been able to find only two other such cases in the literature. The first of these was reported by Davis,¹ whose case at autopsy showed a perforation of a lymphosarcomatous ulcer on the posterior wall of the stomach, and the perforation of a similar lesion in the ileum, near Meckel's diverticulum. The second was Case 5 of Taylor's² series. This patient had two perforations within 13 months. At the time of the first perforation, a biopsy was taken from a regional lymph node as well as from the stomach wall. Both of these showed a typical lymphosarcoma of the reticulum cell type. After the repair of the second perforation the patient was given 1500 r units of roentgenotherapy, and then refused further treatment. He was apparently alive and well six years later.

We have been able to find only two cases in the literature which appear to be of the second group or *formes frustes* type of perforation. One was reported by Keys and Walters,³ in which the perforation was sealed off by the liver, and the other was reported as Cabot⁴ (Case History No 19401), in which the patient had a transient acute abdominal episode which was believed to be due to a lead colic. At a later date, an operation disclosed a lymphoblastoma of the stomach, which had apparently perforated and had become sealed off.

Of the third group there are many examples. They give rise to the statements of Eusterman and Balfour⁵ that a large number of the gastric lymphosarcoma patients, who give histories of gastro-intestinal hemorrhage

have had "ulceration or perforation" Similar statements have been made by Balfour and McCann,⁶ Haggard,⁷ Cheever,⁸ and Diane.⁹

Balfour, in a personal communication, emphasizes that the acute perforations would be observed with greater frequency in general hospitals than in clinics where most of the patients are seen only after reference. McNealy and



FIG 1—Roentgenogram made after recovery from the suture of the perforation, but before the gastric resection. Note the crater and filling defect on the greater curvature.

Hedin¹⁰ have demonstrated the frequency with which carcinoma of the stomach perforates, and have suggested the biopsy of all perforated gastric lesions. It is possible that if this were carried out, more of the acute perforations of gastric lymphosarcomatous ulcers might be found.

Case Report—Hosp. No. 24219-39. B. M., white, male, age 14, was admitted to the Cook County Hospital April 30, 1939. He stated that on the previous evening he had a sudden, sharp, steady pain just to the right of the umbilicus. One hour later he took an enema with fair results. Three hours later the pain had moved to a point in the lower right quadrant. His father gave him small amounts of whisky which aggravated the pain. He did not sleep during the night. The next morning he drank some orange

juice which he immediately vomited. At noon there was a sudden relief of pain for about ten minutes, after which it returned with increased severity all over the abdomen.

The past history was entirely negative, except that in the preceding week he had had two mild attacks of heart burn, which were relieved by soda. The family history was negative for any kind of tumor.

Physical Examination—The patient was a well-developed, well-nourished boy who was acutely ill. Temperature 101.6° F, pulse 88. Examination was negative except for

FIG 2

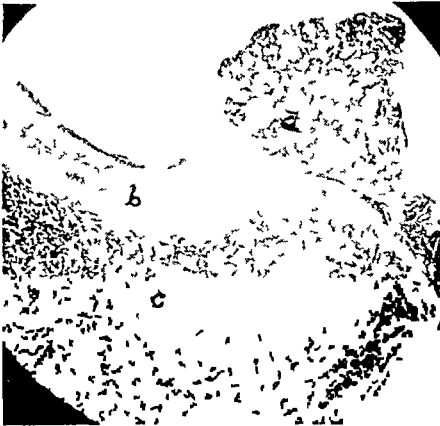


FIG 3

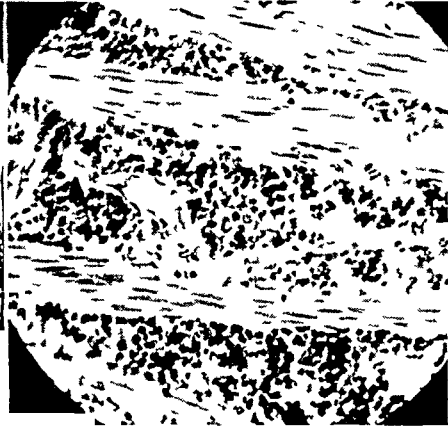


FIG 4

FIG 2—Photograph of stomach removed. Note the ulcerated tumor mass along the greater curvature of the stomach.

FIG 3—Photomicrograph of a section of the ulcerated tumor of the stomach showing the edge of the ulcer (a) composed of gastric mucosa infiltrated with lymphocytes, also the necrotic base (b) of the mass under which are found numerous infiltrating tumor cells (c) ($\times 36$).

FIG 4—Photomicrograph of a section of the tumor mass involving the muscularis propria. Note the side separation of muscle bundles by the tumor cells ($\times 360$).

the abdomen. The abdomen was flat, diffusely rigid, and tender, but this was most marked in both lower quadrants. Rebound tenderness was diffuse. Liver dullness was normal, and the abdomen was silent during a five-minute auscultation. White blood count 25,000, of which 90 per cent were polymorphonuclear cells. The urine was normal and stool negative for blood. Because of the rapidity of the onset of the diffuse peritonitis, a tentative diagnosis of rupture of a Meckel's diverticulum was made, although a perforation at the base of an acute appendix was thought to be more likely, because of the relative frequency of the lesion.

Operation—Under ether anesthesia, a McBurney incision was made. The peritoneum was acutely inflamed. The coils of intestine were markedly injected, and there was

LYMPHOSARCOMA OF STOMACH

a large amount of turbid fluid containing fibrin and mucus. The appendix was full of fecaliths and the serosa markedly inflamed. It was removed, and examination disclosed that the inflammation was serosal only, and secondary to the acute peritonitis. The terminal ileum was explored, but no Meckel's diverticulum found. The wound was, therefore, closed and a right rectus incision made. A perforated ulcer of the anterior wall of the stomach was found. The crater of the ulcer was about 1.5 cm in diameter and the perforation about 5 mm in size. Tissue was removed from the ulcer for biopsy, and the perforation closed. Biopsy was done, both because of the location of the ulcer and the age of the patient. The liver was normal and there were no enlarged lymph nodes palpable. The convalescence was uneventful.

Pathologic Examination—Microscopic Dr A. Ragins: "There are small bundles of muscle tissue separated widely by large hyperchromatic cells with deeply staining round to oval nuclei. The cytoplasm of these cells is very small in amount and the cell membranes are only fairly distinct. In addition to these cells, which are in the majority, one can see eosinophils, polymorphonuclear leukocytes, which are undergoing degeneration, and a few lymphocytes. *Pathologic Diagnosis* Infiltrating lymphosarcoma of the stomach."

Two weeks following the operation a gastro-intestinal roentgenologic study was carried out. This revealed a rather large filling defect on the greater curvature of the stomach (Fig 1). Roentgenograms of the spine, skull and long bones did not reveal any metastases. On the 14th postoperative day, the blood count revealed a hemoglobin of 92 per cent, 4,950,000 erythrocytes, 23,200 leukocytes, of which 74 per cent were neutrophils, 2 per cent eosinophils, 18 per cent lymphocytes, and 6 per cent monocytes. Daily stools were negative for blood. The blood cevitic acid was 0.5 mg per cent.

Second Operation—On the twenty-fourth day after the first operation a transfusion was administered and he was reoperated upon. At this time, the omentum was found to be adherent to the lesion. This appeared as an ulcer in the antral part of the stomach. No abnormal lymph nodes were palpable. A wide resection of the stomach was carried out, and a posterior gastro-enterostomy of the Polya-Reichel type performed. The convalescence was uneventful, and the boy was up on the eighth postoperative day, and discharged to the ambulatory clinic on the tenth day.

Pathologic Examination—Gross "Specimen consists of a stomach portion measuring 13 cm in length and 10.5 cm in the greatest transverse diameter. On the greater curvature there is a raised, firm nodule measuring 2.5×1.5 cm, the central portion of which is ulcerated (Fig 2). The ulcer measures 1.5 cm by 1 cm. The base of the ulcer is light gray, the edges are firm, but are freely movable in places, and light purplish-gray in color. The folds of the stomach are distinct. The omentum is adherent to the serosal surface of the lesion. The lymph nodes are enlarged up to 20 mm and are light yellowish-gray on section. *Microscopic* Sections removed from different portions of the stomach were studied. Those from the serosal aspect reveal large numbers of lipid-filled histiocytes and multinucleated giant cells in the muscularis. These cells were seen around the recent sutures. A section taken through the edge of the ulcerated tumor mass revealed a small portion of the mucous membrane infiltrated by round cells. The base of the ulcer was covered by a necrotic membrane containing cells with a distinct eosinophilic cytoplasm. Beneath the necrotic membrane are numerous lymphoid-like tumor cells which infiltrate the entire thickness of the wall of the stomach (Fig 3). In the muscularis propria the muscle bundles are widely separated by infiltration with the tumor cells (Fig 4).

"The perigastric lymph nodes show a marked hyperplasia with small, distinctly secondary lymph nodes. In places, however, the tissue is composed almost wholly of lymphoid cells. *Pathologic Diagnosis* Infiltrating lymphosarcoma of the stomach."

Subsequent Course—Since discharge from the hospital the boy has been reporting weekly for roentgenotherapy, and has been receiving 180-240 r units through four portals. By October 25, 1939, he had received 7,200 r units. The factors were 200 K V, with 0.5 mm of copper and 1 mm of aluminum filtration. More could not be administered.

because of the patient's susceptibility to roentgen sickness. At this time, he is going to school, participating in athletics, and has no complaints. He has gained 15 pounds since the operation. Repeated gastro-intestinal studies have, thus far, not revealed any recurrence.

COMMENT—This patient represents an acute perforation of a lymphosarcomatous ulcer of the stomach, with a diffuse purulent peritonitis. It is noteworthy that the duration of the symptoms before the acute perforation was only one week. These consisted only of a mild heart burn. When the symptoms of the acute perforation occurred they were similar to those of the perforation of a simple peptic ulcer. This diagnosis was overlooked pre-operatively because of the age of the patient, and because the onset, though sudden, did not appear as severe as with the usual case of gastric perforative peritonitis.

SUMMARY

(1) The term perforation is used somewhat indiscriminately in the literature of lymphosarcoma of the stomach. It would be wise to differentiate between the chronic, *formes frustes*, and acute perforations.

(2) A review of the literature has disclosed but two acute perforations, and two *formes frustes* perforations. This is in contrast to the often repeated statement that perforation is a common complication of lymphosarcoma of the stomach.

(3) Biopsy of gastric perforations may lead to the more frequent recognition of neoplastic processes as the underlying cause.

(4) A case of an acute perforation of a gastric lymphosarcoma is presented where the diagnosis was made from a biopsy at the time of operation. Successful resection was subsequently carried out.

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FORUM

(Articles published in the ANNALS OF SURGERY do not necessarily represent the opinions of the editors, even though they are selected and published with editorial approval. Likewise, the editors may not necessarily be in agreement with correspondents whose communications are important if only because they present stimulating opposition. Since this impartial point of view is vital to progress in science, the ANNALS OF SURGERY offers this forum for pertinent discussions of reasonable length—ED)

Re Abdominal Neoplasms of Neurogenic Origin—by Henry K Ransom, M D, and Earle B Kay, M D

AND

Diagnosis and Surgical Management of Leiomyomata and Leiomyosarcomata of the Stomach—by Frank H Lahey, M D, and Bentley P Colcock, M D (Annals of Surgery, 112, 700-746 and 671-686, respectively, October, 1940)

ARTHUR PURDY STOUT, M D, NEW YORK, N Y

"In the October issue of the ANNALS OF SURGERY there appear two articles on tumors of the gastro intestinal tract, to wit 'Diagnosis and Surgical Management of Leiomyomata and Leiomyosarcomata of the Stomach,' by Frank H Lahey and Bentley P Colcock, and 'Abdominal Neoplasms of Neurogenic Origin,' by Henry K Ransom and Earle B Kay. This latter paper discusses tumors of reputed neurogenic origin in the mesenteric and retroperitoneal regions as well as in the gastro intestinal tract, but it is to the gastric growths especially that I should like to call attention. If one compares the illustrations in the two papers, one cannot fail to be impressed by the close resemblance between the gross appearance of the stomach neoplasms in the two groups, namely, Cases 1 (Fig 2) 3 (Fig 9), 4 (Fig 12), and 5 (Fig 15) in Lahey and Colcock's group, and Cases 1 (Fig 9 A), 2 (Fig 10 A), and 3 (Fig 11 A) in Ransom's and Kay's group. Moreover, clinically, both groups show a marked tendency to ulcerate and give rise to severe hemorrhages. This similarity was remarked upon by Dr Frederick A Collier when discussing the two papers at the meeting of the American Surgical Association, at St Louis, May 2, 1940.

"In my opinion, these are probably not two different tumors but are all neoplasms derived from smooth muscle, *i e*, leiomyomas. In order to support this contention, it will be necessary to acknowledge an erroneous opinion published by me five years ago in a paper entitled *The Peripheral Manifestations of the Specific Nerve Sheath Tumor (Neurilemma)*, Amer Jour Cancer, 24, 751, 1935. When studying the occurrence of this tumor in the gastro intestinal tract, I encountered an article by Gosset A, Bertrand, I, and Lowy, G. *Tumeurs pediculees de l'estomac dites sarcomes* Jour de chir, 23 577, 1924. This pointed out that such tumors were made up of spindle shaped cells with a marked tendency to palisading of nuclei and they insisted that such tumors were derived from nerve sheaths. This paper influenced a number of French and some German authors and it also influenced me, so that I included three gastric neoplasms among a group of 50 neurilemmas. Since that time, I have studied a great many more neurogenic tumors from different regions, and also smooth muscle tumors of the gastro intestinal tract, and I am convinced that the vast majority of such growths come from smooth muscle and not the tissues of the nerve sheath. Briefly, the reasons are these. Neurilemmas are encapsulated—these tumors are not. Nuclear palisading occurs just as frequently in smooth muscle tumors as it does in nerve sheath tumors, therefore, in itself, it is not diagnostic of either tumor. These gastro intestinal tumors show no true division into solid Antoni type A tissue and type B tissue with its microcystic degeneration. Edema and necrosis occur in smooth muscle tumors but they do not produce the microcystic effect. Most important of all, if the tissue is properly fixed and stained, myofibrils can sometimes be demonstrated. There are other reasons, but it would unduly prolong this communication to discuss them in detail.

"These remarks apply only to gastric cases Nos 1, 2 and 3 in Ransom's and Kay's paper. The descriptions given are perfectly compatible with smooth muscle tumors but in my opinion, cannot be interpreted as neurilemmas. I believe that they have been misled by these tumors in much the same fashion as I was misled five years ago. Since I am confessing an error of my own, which five years of study and investigation have taught me to correct, it seemed important to me to offer this critical suggestion so that the same error will not be repeated."

SHIELDS WARREN, M D, BOSTON, MASS

"We are much interested in the similarity of the illustrations in the papers, 'Diagnosis and Surgical Management of Leiomyomata and Leiomyosarcomata of the Stomach,' by Frank H Lahey and Bentley P Colcock, and 'Abdominal Neoplasms of Neurogenic Origin,' by Henry K Ransom and Earle B Kay, which appear in the October issue of the ANNALS OF SURGERY.

"We have read Doctor Stout's letter with much interest and gratification. It is important that palisading of the nuclei, frequently a property of neurogenic tumors, is not, of necessity, restricted to them. The frequency with which the nuclei of the normal smooth muscle of the stomach palisade to a striking degree is familiar to all those doing surgical pathology. Consequently, it is not surprising that palisading is also present in the tumors derived from those same smooth muscle cells. As Doctor Stout points out, the division into Antoni type A and Antoni type B tissue is not clearly brought out in none of the illustrations is a Verocay body clearly demonstrated.

"While we do not deny that neurogenic tumors of the stomach may occur, we feel that at least the first three cases of Ransom and Kay are probably better classified as in the smooth muscle tumor group."

Rebuttal to the Objections of Doctor Stout

HENRY K RANSOM, M D AND EARLE B KAY, M D, ANN ARBOR, MICH

We are pleased to have our attention called to Doctor Stout's communication which concerns the differential diagnosis of neurilemmas and leiomyomas of the stomach, and which presents his most

recent views on this subject. In view of Doctor Stout's painstaking studies extending over a period of many years his opinions should be particularly significant.

The gastric neoplasms described by us in case reports Nos. 1, 2 and 3 and to which reference is made were classified as schwannomas or neurilemmas (Cases 1 and 2) and neurogenic fibrosarcoma (Case 3) on the basis of the following microscopic findings:

(1) The presence of palisading of a characteristic type. This has been described in great detail by Masson (Masson P. Experimental and Spontaneous Schwannomas—Peripheral Gliomas. *Amer Jour Path*, 8, 367, July, 1932) and, presumably, results from the longitudinal division of the Schwann cell nuclei.

The nuclear palisades are ensheathed within anastomotic collagenous prolongations which form a syncytium which can be demonstrated by Masson's tichrome stain. Silver stains show that this syncytium is argyrophilic.

While it is admitted that nerve sheath tumors are not the only neoplasms exhibiting palisades, Masson and others contend that in those of neurogenic origin the elements of the palisade may be shown to possess the specific structure of the schwannian elements whereas in others this cannot be demonstrated.

(2) Whorling and interlacing bands or cords of cells, the appearance of which depends upon the plane of the section through the nuclear bundles.

(3) A reticular type of architecture, found in parts of the neoplasm and which results from microcystic degeneration and edema.

When sarcomatous proliferation of these tumors occurs the original architecture may become largely destroyed and in such cases histologic differentiation becomes increasingly difficult. The diagnosis then often depends upon the preservation in portions of the tumor of the original architecture.

While a perusal of the literature will show that the histogenesis of the nerve sheath tumors has remained a controversial matter, the detailed descriptions given in the papers of Verocay, Masson and others and the evidence presented by them, have seemed sufficiently convincing to warrant the acceptance of their views.

FINNEY-HOWELL RESEARCH FOUNDATION, INC

Announcement has been made by the Finney-Howell Research Foundation, Inc., that all applications for fellowships for next year must be filed in the office of the Foundation, 1211 Cathedral Street, Baltimore, Maryland, by January 1, 1942. Applications received after that date cannot be considered for 1942 awards, which will be made the first of March, 1942.

This Foundation was provided for in the will of the late Dr. George Walker of Baltimore for the support of "research work into the cause or causes and the treatment of cancer." The will directed that the surplus income from the assets of the Foundation together with the principal sum should be expended within a period of ten years to support a number of fellowships in cancer research, each with an annual stipend of two thousand dollars, "in such universities, laboratories and other institutions, wherever situated, as may be approved by the Board of Directors."

Fellowships carrying an annual stipend of \$2000 are awarded for the period of one year, with the possibility of renewal up to three years, when deemed wise by the Board of Directors, special grants of limited sums may be made to support the work carried on under a fellowship.

Applications must be made on the blank form which will be furnished by the Secretary or any member of the Board of Directors.

October 16, 1941

BOOK REVIEWS

FELDCHIRURGIL. LEITFADEN FÜR DEN SANITÄTSOFFIZIER DER WEHRMACHT Edited by H. Kafer, M.D., Second Edition Dresden Theodor Steinkopff, 1940 Price 9 Reich marks

THE TITLE OF THIS BOOK IS "Field Surgery A Guide for Medical Officers of the Military Forces" The book is just that! It is a pocket manual of 372 + vi pages, $5\frac{1}{2} \times 7$ in in size, written for front-line surgeons It discusses matters of organization, transportation and general and special surgery, of interest to medical officers in the combat zone, it stops at an echelon corresponding to our Evacuation Hospital The edition is dated September, 1940, and includes some material gathered from the rapid advance of the German armies through Poland The announcement truly states that it is not a textbook, but a short handy guide, to enable medical officers of the line and officers surgically active in advanced units to form a rapid, reliable and comprehensive judgement of the varied and sudden measures they may be called upon to undertake The editor and his staff of ten collaborating military surgeons have, on the whole, fulfilled their purpose admirably, some chapters are outstanding, and few are less so

The general part contains chapters on military matters—organization, tactics, weapons and their effects, transportation—and on general field surgery (general technic in the field, first aid, infection, collapse and shock, anesthesia and hemorrhage) The second part is a concise regional field surgery, treating of wounds of the cranium, the face and eyes, ears, mouth, jaws, the neck, the chest, *etc*

The book is so concise, meaty and full of interest, especially to those with military experience, that it is not possible to comment *seriatim*, on all its contents Some details, however, are especially striking to the American reader

It is noteworthy that the German Army seems still to maintain the rather divided medical echelons that it had prior to the First World War, whereas other armies have tended to omit units, or to condense them whenever possible However, the chapter on organization does mention the need of flexibility in the establishment of various dressing stations and hospital units, and stresses the need of placing field hospitals further to the rear, which all observers in rapidly moving warfare are aware of The statement that field hospitals are scarcely useful unless they can maintain their position for at least a week, would indicate that the author was fortunate enough to have acted mainly with advancing rather than retreating troops The same is true of the statement that only 10 per cent of men operated upon can be evacuated on the first postoperative day, and a further 20 per cent on each of the succeeding days It seemed to the reviewer, during his experience in the Spanish Revolution, that many wounded were more fit for evacuation immediately after operation than they were during the next two or three days succeeding

Folsch's chapter on general surgical technic is outstandingly good, and is evidently the product of great practical experience and adaptability It is strange to find that he omits chloride of lime from his list of antiseptics, and that neither he, nor other collaborators, mention the Orr technic which other armies have found so useful

The German mobile surgical team consists of eight men 5 sterile—1 surgeon, 2 assistants, 1 instrument helper, 1 dressing helper, 3 unsterile—1 anesthetist, 1 roustabout, 1 sterilizer Few armies will be able to afford such abundance of trained personnel!

Active immunizations against tetanus and treatment of gas and anaerobic infection are not mentioned No mention is made of plasma transfusion, there is a short paragraph on the transfusion of preserved blood, but there seems to be no provision for blood-banks serving the front However, a note in the section on the choice of donors would indicate

that each German soldier has his blood group determined and entered in the booklet he constantly carries on his person

There is no space for comment on the section on Regional Surgery, it may, however, be noted that Gohrbandt's excellent chapter on abdominal injuries, although they make up less than 5 per cent of the wounds treated, is 55 pages long, while the chapter on extremity injuries, which make over 80 per cent, consists of only 26 pages. This chapter is distinctly disappointing. It is vague and lacks concrete and specific directions, it describes methods we are inclined to mistrust, or consider as antiquated, it fails to mention others (Willems' treatment of joint injuries, Orr treatment of compound fractures, etc.), which we prize highly.

On the whole the book is an epitome of those qualities that have made the German military machine so successful—direct, short, explicit, complete. One can but hope that a similar book may appear in English. This little volume, supplemented by Franz's classical small text, gives a doctor, called upon to perform military surgery in almost any position, nearly everything he need know. Weightier volumes and small systems of surgery may interest students in military schools and leisurely officers at base hospitals—but Franz and Kafer are of real use where help is scarce and urgently needed, *viz*, at the front.

LEO ELOESSER, M D

SULFANILAMIDE AND RELATED COMPOUNDS IN GENERAL PRACTICE By WESLEY W SPINK, M D Chicago Year Book Publishers, Inc., 1941

This manual of somewhat over 200 pages contains a discussion of the sulfonamides designed primarily for the general practitioner. It fulfills its purpose admirably. It deals clearly and briefly with such fundamental problems as chemical structure in relation to anti-bacterial activity, mode of action, and pharmacologic behavior.

The main purpose, however, has been to answer the problems of choice of preparation, diseases best treated, doses and toxic effects which arise daily in practice. The local use of the sulfonamides in surgery, dermatology and dentistry is discussed. Prophylactic use in a variety of diseases is considered.

The book is written by an obviously careful, conservative and judicious author with personal experience in this field. The fact that it is concerned primarily with sulfanilamide, sulfapyridine and sulfathiazole, and has little to say of sulfadiazine or sulfalylguanidine is not a criticism but merely a limitation inherent in any book dealing with this rapidly changing subject.

KENDALL A. ELSOM, M D

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